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Comparison of Corticosteroid Injections and Platelet-Rich Plasma (PRP) Injections in Improving Symptoms of Osteoarthritis of the Knee

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COMPARISON OF CORTICOSTEROID INJECTIONS AND PLATELET-RICH PLASMA (PRP) INJECTIONS IN IMPROVING SYMPTOMS OF OSTEOARTHRITIS OF THE KNEE

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Abstract

Background: With the growing prevalence of knee osteoarthritis (OA) in the United States and the rising costs of associated surgery, there has been an increase in the amount of research dedicated to alternative treatments. These treatment options may include various types of injections to the knee.

Purpose: The purpose of this critical review is to consider how corticosteroid injections compare to platelet-rich plasma (PRP) injections in terms of efficacy in improving symptoms of pain and effusion of the knee in patients with knee osteoarthritis.

Results: A total of 17 articles were chosen from databases, including Google Scholar, CLIC, and PubMed. These were assessed using the appropriate tools given the type of article. Trends of the literature identified in this review showed that PRP injections may have longer-lasting effects than those of corticosteroid injections and may also be more effective in patients with early stage osteoarthritis.

Conclusion: This critical review of the literature had the purpose of determining the efficacy in reduction of symptoms, pain, and effusion in patients with knee arthritis through the use of corticosteroid injections or PRP injections. Through this review, it was concluded that PRP injections may be more useful for long-term relief of symptoms associated with osteoarthritis of the knee, especially for those in the early stages of this disease. In future research, a focus should be placed upon studying corticosteroid injections versus PRP injections and should compare the efficacy through a double-blinded randomized controlled trial to further investigate these treatments.

Implications for Research and Practice: As PRP injections seem to provide better long-term relief of symptoms such as pain and increase function of the knee, it would be beneficial for a patient to consider this as a treatment option for osteoarthritis of the knee, especially if they are within the early stages of arthritis. Implications for the athletic training practice may include the discussion of this among other treatment options with health care providers to establish best practice standards along with furthering the needed evidence to allow more major insurance providers to cover PRP as a treatment for knee osteoarthritis.

Keywords: platelet-rich plasma injections, corticosteroid injections, knee osteoarthritis treatment

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Chapter 1: Introduction

Need for Critical Review

In recent years, treatment options for osteoarthritis of the knee, other than total knee arthroplasty (TKA), have been developing as TKA tends to be one of the most expensive and burdensome procedures in treating OA (Glynn et al., 2018). The Centers for Disease Control and Prevention (CDC) have reported that there are about 54.4 million adults in the United States who have been diagnosed with a form of arthritis from 2013-2015. The CDC also estimates that by 2040, there will be as many as 78 million people with this diagnosis. (Centers for Disease Control and Prevention, 2018).

Research in recent years has begun to focus on alternative treatments to combat the rising costs of surgery along with reducing the possible risks associated with surgery through more conservative interventions. The purpose of this study is to analyze the current research on how PRP and corticosteroid injections affect pain and effusion in the knee. This knowledge will be beneficial when providing recommendations to patients regarding their treatment options for their diagnosis of osteoarthritis of the knee and provide furthering the understanding of the efficacy of each. The question considered in this research is, how do corticosteroid injections compare with Platelet-Rich Plasma (PRP) injections in improving symptoms of pain and effusion of the knee in patients with osteoarthritis of the knee?

Significance and Mechanism of Treatments

In the athletic training setting, there is great importance in understanding the efficacy that different treatment options have on osteoarthritis of the knee. Osteoarthritis is a problem that is

expected to grow, along with the costs of health care and invasive procedures (Centers for Disease Control and Prevention, 2018). Athletic trainers can advocate for their patients to pursue the most effective treatment at the best value. With conclusive studies on alternative treatments, health insurance companies will be convinced in the efficacy of the treatment, and thus, increase coverage likelihood (Jones, 2018).

According to the Mayo Clinic, corticosteroid injections are most often used to treat inflammatory or osteoarthritis in joints. They typically consist of a corticosteroid medication and a local anesthetic and are performed by a physician for pain relief, inflammation relief, and diagnostic purposes. They are often limited to once every 6 weeks with no more than 4 times per year, due to concerns that this type of injection may cause further cartilage deterioration when used frequently (Mayo Clinic, 2019). Platelet-rich plasma injections are unique in that the patient's own body materials are used without synthetic properties (Glynn et al., 2018). The injections are performed by drawing the patient's blood and using a centrifuge to spin down a concentrated solution of platelets. That solution is then injected into the capsule of the knee and acts as a kick-starter for the body's natural inflammatory process (Platelet-Rich Plasma (PRP) Injection: How it Works, n.d.).

Macrophages and monocytes are the main players in the inflammatory process, leading to wound healing. Monocytes are recruited initially to the site of injury and continue to promote low levels of inflammation (Koh et al., 2011). This process proceeds with removal of cell debris, pathogens, and any damaged tissues, allowing for the proliferation and repair stages of healing. Signs of inflammation in the body include redness, heat, swelling, and pain (Wassung, 2012.). It is important to know the process of inflammation in relation to PRP, so that the process of inflammatory healing can be better understood. Since inflammation is the body's way of healing,

these injections should be effective (Koh, 2011). However, various studies show there have been mixed results. Previous studies report that PRP may only be effective in patients in the early stages of osteoarthritis, rather than those with advanced degeneration (Chang et al., 2011; Jang et al., 2012). Patel et al., (2013) agrees that PRP is most effective in those in the early stages of knee arthritis but suggests that its effects are lost 6 months following the treatment.

Kellgren-Lawrence is typically the classification system that is used to assign severity from Grade 1 to Grade 4 to knee osteoarthritis based upon radiographs. Grade 1 is given to radiographs which demonstrate marginal joint space narrowing and osteophyte formation. Grade 2 may still show minimal joint space narrowing and osteophyte formation, but this is more advanced than Grade 1 but less than Grade 3. In the classification of Grade 3, there is defined narrowing and moderate formation of osteophytes and in Grade 4 there is advanced joint space narrowing and large osteophyte formation (Kohn, 2016).

A study published in 2017 by Hamdy et al., investigated the similarities and differences between hyaluronic acid (HA) injections and corticosteroid (CS) injections, and in 2016, a study by Askari et al. demonstrated how these two injections compare, but neither addressed the use of PRP injections in patients with knee OA. This could be due to the lack of information there is regarding PRP injections, making it difficult to reach a conclusion comparing the effectiveness to CS injections. Since PRP is becoming a more common method of treatment, more studies are being conducted, posing further questions about the process and its efficacy.

Piuzzi et al. conducted a study in 2019, which analyzed the cost and efficacy that was claimed by 179 clinics across the United States. A unilateral PRP injection in the knee had a mean price of $714 with a standard deviation of $144. Meaning that a single PRP injection in the

knee could range from $570 to $858 (Piuzzi et al, 2018). Due to a lack of conclusive evidence regarding PRP injections, the injections are not typically covered by most health insurance programs (Nall, 2017). As for corticosteroid injections, the cost tends to be lower than PRP and is often covered by most health insurance plans. However, for those without health insurance, a corticosteroid steroid injection into a joint can cost $100-$300 per injection. Depending on the patient's specific health insurance plan, this cost may be partially or entirely covered (Watts, 2019). For instance, Summit Orthopedics, an orthopedic clinic system in Minnesota and Wisconsin, reports that while they will attempt authorization of PRP injections, they are still largely not covered by most health insurance companies. However, they will provide them for self-pay or use of their Health Savings Account (HSA) (Summit Orthopedics, n.d.). According to a study by Jones et al. conducted in 2018, PRP is not 'FDA-approved' but is still offered as a treatment method for various conditions. This study suggests that PRP improves symptoms in patients, but it does not have the statistical support. Therefore, further research of PRP as a treatment method is needed (Jones, 2018).

There are risks associated with both injections. PRP injections may carry the risk of reaction to the local anesthetic, infection, or excessive bleeding. However, since the injectant is autologous, meaning that it has been obtained from the same person, there is not a risk of immunological reactions, such as rejection (Glynn et al., 2018). Due to the numerous different types of steroids that can be used in this process, there is a wide range of side effects depending on the corticosteroid used. Some of these side effects include infection, nerve damage, temporary flare of pain, osteoporosis, cartilage damage, and increased blood glucose levels which is a specific risk factor in diabetic populations (Mayo Clinic, 2019).

Summary

In looking to the future, it would be helpful for an athletic trainer to have a good basis of information regarding the different types of treatments available for a multitude of injuries. It is important for athletic trainers to understand the uses, efficacy, and prognosis for those with knee osteoarthritis using one of these types of injections as treatment. By gaining further understanding, athletic trainers can advocate for their patients among the rising prevalence of osteoarthritis and growing health care costs as well as pioneer new research in an effort to gain more health care coverage of emerging treatments.

Chapter 2: Methods

The purpose of this chapter is to discuss the processes and methods utilized to obtain scholarly articles and other research to determine the efficacy of cortisone injections and platelet-rich plasma injections in reducing pain and effusion in osteoarthritic knees. In the beginning stages of researching this topic, databases including Google Scholar, PubMed, and CLIC (Cooperating Libraries In Consortium) were used to gather literature. Results were limited only to peer reviewed sources which were published within the last 10 years with access to the full article. All articles with key phrases or words in the titles were screened for significance in relation to the topic and in quality of research prior to being included in this study. The articles gathered were then appraised using the PEDro Scale for randomized controlled trials, Critically Appraised Topic (CAT) Manager Appfor Systematic Reviews and Mata-Analysis', and Currency, Relevance, Authority, Accuracy, Purpose test (CRAAP test) or diagnostic studies. Each article was selected to represent a comprehensive and thorough view of each type of injection and to provide the most factual information regarding their efficacy in the improvement of pain and effusion in patients with knee osteoarthritis.

Search Strategies

Across the databases, multiple different arrangements of the keywords, "corticosteroid", "hyaluronic acid", "platelet-rich plasma", PRP", "injection", "knee osteoarthritis", "treatment", "efficacy", "pain", and "effusion" were used to cultivate the resulting literature. For example, a search of Google Scholar on 01/13/2020 was conducted using a number of key phrases to assess the population of articles available. The phrase "corticosteroid injections in knee osteoarthritis" yielded about 18,100 results and another search using "PRP injections in knee arthritis yielded

about 9,270 results. The phrase “hyaluronic acid injections versus corticosteroid in knee osteoarthritis” showed about 11,300 results, while “PRP injections versus corticosteroid in knee osteoarthritis” only showed about 5,020 results. When “injection” “PRP”, “hyaluronic acid” and “corticosteroid” were searched in conjunction with “efficacy”, there were about 17,300 results, 36,600 results, and 17,500 results, respectively. A similar strategy was used with PubMed and CLIC which then yielded similar results. The initial purpose of this research was to explore the efficacy of cortisone injections, PRP injections, as well as hyaluronic acid injections. As indicated by the limited search results surrounding hyaluronic acid injections, the decision was made to shift the focus of this study to only corticosteroid injections and PRP injections.

Inclusion and Exclusion Criteria

When searching databases, all were set to show results published between 2009-2019 to ensure the most updated information. While using Google Scholar, additional search filters were not available which made it difficult to find sources that included the full text of the article. Additional filters including full text and publications in English were utilized for the PubMed searches and filters including full text online, peer reviewed journals, and publications in English were used for CLIC search. A specific country of study, area of the world or clinical setting was not specified; therefore, the included literature is from a variety of settings. Articles that were not available in full-text, were not written in English, were not peer reviewed, or were published prior to 2009, were excluded. The exclusion criteria were used in order to reduce the number of irrelevant literatures concerning this topic, ensure the highest-quality literature, and to allow for the most comprehensive literature review.

Evaluation

The literature was appraised and quality was assessed using the PEDro Scale (Appendix B) for randomized controlled trials, CAT manager Appfor Systematic Reviews and Mata-Analysis' (Appendix C) and quasi-experimental time series study (Appendix D), the CASP tool (Appendix E) for prognostic studies, and CRAAP for diagnostic studies (Fineout-Overhold et al., 2010). The PEDro scale includes criteria that evaluates for eligibility criteria influencing external validity, random allocation of subjects to groups, concealed allocation to groups, similar prognostic factors at baseline, blinding of subjects, blinding of treatment administrators, blinding of assessors, at least one main outcome is measured from at least 85% of initial subjects, all subjects who had outcomes measures received a treatment or a control, statistical comparison is reported for at least one main outcome, and measures of variability are provided for at least one main outcome (PEDro scale, n.d.). The PEDro scale is then graded on a range of 0-10 points. Scores given in the range of 9-10 are "excellent", 6-8 are "good", 4-5 are "fair", and 0-4 are "poor". The CAT (Critically Appraised Topic) App uses cause and effect questions to determine the level of trustworthiness of certain pieces of literature from academic journals. Based upon the answers given for those questions, it is rated either very low (level D-), low (level D), limited (level C), moderate (level B), high (level A), or very high (level A+) (CAT Manager App, n.d).

The Critical Appraisal Skills Programme (CASP) is used to evaluate prognostic studies and aims to determine how certain risk factors influence the future outcome or prognosis of a specific condition. It allows the evaluator to systematically explore how the study rates, specifically in its validity (CASP Checklists, 2020). The CRAAP Test evaluates for Currency, Relevance, Authority, Accuracy, and Purpose of the study presented. Currency refers to the date that the literature was published and of any revisions. Accuracy takes the reliability and

correctness of the information based upon where the information is from, the evidence with which it is supported, and the presence or lack of bias. The importance of the information in relation to the topic is assessed by relevance through the investigation of the intended audience and the language used. The purpose is in reference to the reasoning for the information, the point of view of the information, and the authors' intentions for the information being presented. The authority of the literature is determined by the credibility and qualifications of the author and publisher, organizational affiliations, and whether the author or publisher can be contacted (Research Guides: Evaluating Sources: The CRAAP Test. n.d.).

Summary

In conclusion, a total of seventeen articles were chosen using the above stated inclusion and exclusion criteria while searching various databases. Six randomized controlled trials, four systematic reviews, three systematic reviews and meta-analyses, two prospective randomized studies, one diagnostic study, and one quasi-experimental time series analysis were all included within the 17 articles used. Then, each article was reviewed and appraised using an appropriate method based upon the type of article. These methods were carried forth with the intention of supplying the most current, relevant, and comprehensive information regarding the efficacy of corticosteroid injections, hyaluronic acid injections, and platelet-rich plasma injections.

Chapter 3 – Literature Review and Analysis

Synthesis of Matrix

The articles utilized in this study are laid out in a matrix format for organization purposes and for easy identification (LibGuides: Matrix Method for Literature Review: The Review Matrix. n.d.). In this context, the matrix identifies the citation of the source, the method of research, the purpose of the study, the sample and setting of the study, the design instruments, the results of the study, what recommendations can be made based upon the data, and finally, the results of the chosen quality assessment for each article. This information allows the reader to quickly assess an article and compare it to others included in this research. The information included is meant to provide a synopsis of the data found in each article. See Appendix A. There are a total of 17 articles reviewed and included in the matrix. These include three systematic reviews, two quasi-experimental time-series analyses; one randomized controlled trial, two prospective studies, and 1 meta-analysis and systematic review.

Synthesis of Major Findings

Seventeen articles were reviewed for data regarding this question whether it is in support or disagreement with either corticosteroid injection or PRP injections. Each article considered was then assessed using one of the previously stated assessment tools to determine the reliability for the recommendations made in this study. The articles will be discussed in order of quality and relevance of information provided for the purpose of this study.

A prospective, randomized, double-blinded clinical trial was conducted by Jubert et al. (2017) regarding the use of platelet-rich plasma injections in subjects with advanced knee

osteoarthritis. It was hypothesized that PRP could reduce pain and lead to effective functionality of the knee joint more effectively than with corticosteroid injections. A total of 75 voluntary patients with Kellgren-Lawrence Grades 3-4 osteoarthritis of the knee were included in the study and randomly sorted into treatment groups. These groups included leukocyte reduced PRP or an intraarticular corticosteroid injection. Inclusion criteria required that participants were between 40-80 years old, had knee osteoarthritis, were eligible for a total knee arthroplasty (TKA), had the ability to walk, had a baseline VAS score greater than 60, and had the ability to give informed consent. Subjects were excluded if they did not meet the inclusion criteria, had a history of arthroscopic surgery in the previous 3 months, received injections (corticosteroid, anesthetics, or hyaluronic acid) in the previous years, or had a chronic medical condition. The procedure for both types of injections were performed under sterile conditions and 4 mL of the given treatment was injected to the medial compartment of the knee without local anesthetic. To decrease bias, this process was double blinded for both the subject and injector. Both groups were able to use painkillers and NSAIDs as needed during the study period. Each subject then followed-up 1 week, 1 month, 3 months, and 6 months for recheck and evaluation. Then, each was evaluated using the VAS, Knee injury and Osteoarthritis Outcome Score (KOOS), and Short Form-36 to assess quality of life (Collins el al., 2011; Hawker et al., 2011). No adverse effects were noted, and there were no noted differences in patients who used painkillers or NSAIDs. In the treatment group (PRP) there was a higher rate of patient satisfaction at 6 months, but it was not statistically significant ($p = 0.472$). There was a noted decrease in VAS scores in both groups, but in considering the baseline scores of each group, the PRP group tended to have a greater decrease in these scores, but was once again, statistically insignificant ($p > 0.05$). Due to a lack of statistical significance, the results of this study did not confirm its hypothesis regarding

a greater benefit of corticosteroid injections. It could be concluded that PRP did tend to improve symptoms of pain and increase functionality in patients with knee late-stage osteoarthritis; there is no reported greater benefit than corticosteroid injections. Further research should be conducted in order to provide further evidence of the benefits of PRP versus corticosteroid injections (Jubert et al., 2017). This randomized controlled trial is of high quality based upon the PEDro scale with a score of 11/11.

Nabi et al. (2018) published a randomized controlled trial with the aim of this study to evaluate how PRP injections and corticosteroid injections compare in effectiveness to control pain in patients with knee osteoarthritis. This study decided to use triamcinolone as the corticosteroid of choice. Patients included in this study had Grades 2-3 knee osteoarthritis and were seen in the Guilan University of Medical Sciences from April 2016 through June 2017. Patients were included if they were 20-75 years old, had diagnosed grades 2-3 knee osteoarthritis, and had knee pain for at least 3 months without improvement from other interventions. Patients were excluded if they had knee joint deformities, cancer, rheumatoid arthritis, BMI greater than 35 kg/m^2, pregnant or breastfeeding, infection, blood abnormalities or disorders, among other chronic conditions. A total of 67 patients participated in this study. They were sorted randomly into either the corticosteroid group, Triamcinolone, or the PRP group. Each participant received his or her injection under ultrasound once per month for 3 months. Then pain was evaluated using the Visual Analog Scale (VAS) and the Knee injury and Osteoarthritis Outcome Score (KOOS) each month for 3 months and then 6 months following the conclusion of the treatment. There were lower scores in pain on VAS in the PRP group compared to the Triamcinolone group. Statistically significant ($p=0.385$) results were found at 2, 3, and 6 months follow-ups. There was also improved quality of life, functions of daily living,

and overall improved symptoms indicating that PRP may be the superior treatment in decreasing pain and improving these other factors (Nabi et al., 2018). This randomized controlled trial is of high quality based upon the PEDro scale with a score of 8/11 signifying “good: quality Limitations of this study included lack of concealed allocation and lack of blinding due to ethical reasons in treatments given.

Malahias et al. (2018) conducted a study regarding the efficacy of platelet-rich plasma versus corticosteroid intra-articular injections for a treatment option for trapeziometacarpal arthritis. This study began with 48 patients who all had grades 1-3 osteoarthritis of the first CMC joint and had been examined between July 2012 and December 2014. Patients were excluded if they had rheumatic disease, comorbidities of the hand, history of gout, previous surgery to the affected hand, or an injection in the last 12 months. After elimination due to exclusion criteria, there were 33 patients who remained to participate in the study. Each participant signed an informed consent form and each was then randomly assigned to one of the two groups. One group received 2, ultrasound guided PRP injections, 2 minutes apart, while the other group received 2 ultrasound guided injections, 15 minutes apart, of methylprednisolone and lidocaine. Each patient then followed up at 3 months and 12 months and was evaluated based upon the Visual Analogue Scale (VAS), and the Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH). Both the patient and the physician during evaluation were blinded. In comparison with the corticosteroid injection, the group who had the PRP injection had statistically better improvement of their VAS scores ($p=0.015$) and Q-DASH scores ($p=0.025$). It was concluded in this study that corticosteroids offer better short-term relief, but PRP injections may be the better treatment option for long-term relief (Malahias et al., 2018). This randomized

controlled trial is of high quality based upon the PEDro scale with a score of 10/11 Limitations of this study included lack of blinding of all subjects.

An additional systematic review, by Maricar et al. (2012), was identified and had the purpose of exploring the factors that determine the possible response to corticosteroid injections in a patient with knee osteoarthritis. The researchers questioned whether the factors that influence the response to these injections are related to the patient, treatment, or the disease. The databases Medline, Embase, AMED, CINAHL, Web of Science, and Cochrane Central Registers were searched for articles up until January 2012. The terms used when searching included “knee osteoarthritis”, “intra-articular”, “corticosteroids”, “injection”, “trials”, and “procedures”. Articles that were chosen to be included had subjects who were over the age of 18 and who had been diagnosed with knee osteoarthritis by clinical assessment or evaluation with radiographs. Factors used to evaluate for a response to the injections included knee effusion, clinical synovitis, synovial hypertrophy, presence of knee pain, knee range of motion, muscular strength, stiffness, local tenderness, heat, symptom duration, and certain mental health factors. Improvement of pain, measured on The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), was the major factor on which this study focused. The search of the included databases yielded 696 articles, which were filtered down due to duplications and exclusion criteria, which is not clearly stated within the written report. After reviewing 101 articles, 65 full-text articles were then reviewed and a total of 11 were found to meet the inclusion criteria set forth by the study, of which 10 were randomized controlled trials and one was an observational study. Due to differing factors in each study such as, outcome measures, predictors, criteria of symptom changes, and missing data, it was not possible to pool the data and therefore difficult to form conclusive and consistent results. However, it was concluded that

the presence of effusion, aspiration of fluid from the knee, severity of disease, absence of synovitis, and injections given under ultrasound guidance may result in a better chance of response to steroid injections to the knee joint. Since the study had a rather small sample size along with inconsistency in the results from each article, it was stated that further and larger-scale research would be needed for conclusive results to be given regarding the factors contributing to outcomes from this type of injection (Maricar et al., 2012). When evaluated by the CAT Manager app, the design of this article was found to be very appropriate at level A+. The effect size and confidence interval were not reported, which is a limitation of this article. The trustworthiness of this article is still very high at 95% and rated very high quality based upon the CAT Appappraisal.

In a systematic review conducted by Ben-Nafa et al. (2018), the effects of corticosteroid injections versus platelet-rich plasma (PRP) injections were explored in patients with lateral epicondylitis. They hypothesized that PRP injections would provide more long-term therapeutic effects than corticosteroid injections along with fewer complications. The study selection criteria focused on randomized controlled trials, but all studies were considered for inclusion in the study. A search of 11 databases including Web of Science, Scopus, PubMed (MedLine), ScienceDirect, CINAHL, EMBASE, Ovid, NICE, Physiotherapy Evidence Database, Cochrane Library and ClinicalTrials database was utilized to locate the 732 articles considered. After excluding duplications, review articles, and conference papers, among other irrelevant studies to the topic, there were 43 remaining studies to be considered. Articles not written in English articles published prior to 2005 were excluded along with articles including patients with elbow pain other than lateral epicondylitis and patients who had other injections. After further review of the full-text articles, a total of 5 randomized controlled trials were included in this systematic

review, which included 250 patients. Clinical findings showed that while corticosteroid injections provided faster symptom relief, they did not have the long-lasting effect that PRP injections showed. Cost-effectiveness was also considered and it was found that PRP injections can cost as little as $840 and as much as about $1000, but corticosteroid injections are typically about one-third the price of PRP. However, since corticosteroid injections were shown in this study to have a shorter length of effectiveness than PRP, the potential for repeated cost in corticosteroid injections is higher. In terms of complications, no major adverse effects were reported and therefore the rate of complications is difficult to definitively assess. The articles in this study were randomized controlled trials and were therefore considered reliable due to the nature of the study design. However, it should be noted that there is a risk of potential bias with 2 of the included articles. These studies were conducted out of teaching hospitals, but there were multiple details regarding the patient population, which were omitted and therefore create the potential for bias. These studies were also conducted in a two-stage design rather than creating separate studies, which also creates the potential for bias. One study did not disclose population demographics and another 2 of the 5 included studies did not explain the randomization and allocation process of subject selection. This calls the quality of the research method into question, especially since these articles claim to be randomized controlled trials. With these limitations in mind, this study provides the conclusions that corticosteroid injections may be beneficial for fast and short-term relief of lateral epicondylitis, but PRP tends to be more effective for the treatment of symptoms in the long term. Regarding the efficacy of corticosteroid injections versus PRP injections in patients with knee osteoarthritis, it is difficult to discern whether the conclusions made in the systematic analysis would be applicable to the knee joint. Further research would need to be conducted in order to determine if this article provides

plausible support for this study's topic (Ben-Nafa et al., 2018). The design is very appropriate at level A+ when evaluated by the CAT Manager app and it was concluded that this article is 95% trustworthy. There is no reported effect size of CI and therefore it is difficult to assess precision.

A prospective, randomized study by Huang et al. (2019) investigated the efficacy of corticosteroid injections, platelet-rich plasma (PRP), and hyaluronic (HA) injections with the goal to determine if one is superior to another. There were 265 possible subjects reviewed and 120 met the inclusion criteria of symptomatic knee osteoarthritis, were between 40-65 years old, had a BMI less than 30, had stable knees with normal alignment. Subjects were excluded if they had tricompartmental knee osteoarthritis, rheumatoid arthritis, associated hip osteoarthritis, previous tibia osteotomy or cartilage transplant, effusion of the knee requiring aspiration, among other chronic diseases. All 120 patients were randomly placed into either the PRP, corticosteroid, or HA treatment groups and assessed with the WOMAC scale at 3, 6, 9, and 12 months which was then compared the baseline WOMAC score taken prior to treatment. The VAS was also used to assess pain both prior to treatment and at the 12-month follow-up. When comparing the WOMAC scores, there did not seem to be any major differences in the 3 groups at the 3-month follow-up post-injection. However, the subjects who received PRP injections had statically significant ($p < 0.05$) improvement in the WOMAC scores at the 6, 9, and 12-month marks. Therefore, it was concluded that PRP injections for osteoarthritis of the knee in its early stages may be a reasonable option for treatment when compared to corticosteroid injections and HA injections. This study supports the use of PRP injections in patients with knee osteoarthritis and is useful in support of the question posed by this research. It may be reasonable to conclude that PRP is best utilized in the early stages of knee osteoarthritis, although the treatment may take longer than 3 months to show a noticeable difference in symptoms (Huang et al., 2019). In

appraising this article using the CASP (Critical Appraisal Skills Programme) tool it was found that 10/11 questions were answered with “yes”, indicating that this article is likely trustworthy. The remaining questions could be answered with evidence from the article. Participants were recruited and approved by an ethics committee. This particular study was randomized in distribution and analysis to minimize bias. Confounding factors, which may have contributed to limitations of the study, were identified and accounted for but were not prevented. These results can be applied to a local population, especially in an orthopedic setting in those in the early stages of osteoarthritis.

A double-blinded randomized controlled trial was conducted by Duif et al. (2015). It set out to investigate how leukocyte-poor PRP injections affect degenerative lesions and symptoms in knee osteoarthritis when injected during knee arthroscopy. Patients who were seen between January 2010 and December 2011 who had non-traumatic knee pain, image diagnosed osteoarthritis of the knee, and had failed conservative treatment after 12 weeks and now considering arthroscopic surgical intervention were eligible to be included in this study. Patients were excluded if they were unable to provide informed consent, had circumscribed chondral damage, infection, rheumatologic disorders, corticosteroid injection within the last 3 months, collateral ligament instability greater than grade II, immunosuppression, cancer, or other serious conditions. A total of 58 patients were chosen for this study with 24 in the PRP group and 34 in the control group. All patients had knee arthroscopy performed and after interventions were completed, depending on the assigned group, the patient was given either the placebo or PRP injection. All patients were closed in the same protocol and were allowed to fully weight bear immediately. Doctors ensured double blinding as each followed the same follow-up procedure for both groups. Pain, function, and quality of life were assessed at baseline; 6-week, 6-month,

and 12-month follow up using the Visual Analog Scale (VAS) and SF-36. A total 5 patients were lost to follow-up, leaving 91.4% of patients who initially were enrolled in the study. At the 6-month follow up, pain was lower in the PRP group (p-value=0.008). However, at the 12-month follow up the control group had lower scores of pain (p-value=0.063). It should also be noted that the quality of life in the PRP group at 6-weeks and 6-months was significantly higher than that of the control group, but this was equal between the groups at the 12-month follow up. From this information, it can be concluded that intraoperative application of PRP, specifically leukocyte-poor PRP, may improve pain and knee function within the 6-12-month span following the treatment when compared to interventions with only arthroscopy (Duif et al., 2015). This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as "Yes" indicating that this article is of excellent quality.

In a systematic review and meta-analysis published in 2017 by Singh et al., platelet-rich plasma (PRP) versus corticosteroid injections as a treatment for plantar fasciopathy was studied and reported. The purpose of this study was to determine if there is an association between either of these two injections with improved pain or improved function. The databases MEDLINE (Pubmed), Excerpta Medica, and Ovid were used with the keywords "platelet rich plasma", "PRP", "plantar fasciitis", "plantar fasciopathy", "corticosteroids", "steroids", "injection", "visual analogue score (VAS)", and "quality of life". Articles included in the meta-analysis fit the comparative purpose of the study, were a randomized controlled trial, prospective observational or retrospective study, reported scores on quality of life, or pain, or VAS scores, include patients without previous surgical history for plantar fasciopathy, and had at least 10 patients in a given group. Exclusion criteria included lack of pain or quality of life score, case reports, abstracts, reviews, studies with patients with a systemic disease, and if the article was

not published between January 2000 and September 2016. After applying these inclusion and exclusion criteria, 10 publications were included in the meta-analysis including 517 total patients. The data extraction process sought to find the pain and function scoring for patients at the 3-month and 6-month follow-up after receiving the injection. At the 3-month follow-up, subjects who had PRP injections had improved VAS scores, but at the 6-month follow-up there was no major difference reported. In addition, there were no significant differences in pain or functional scores at the 12-month follow-up. With these results, it was concluded that PRP injections for plantar fasciopathy might be helpful in the short-term, but do not show good improvement in the long-term. However, since little information was provided regarding adverse events, costs, and a sample size of only 10 publications, further large-scale research is needed to draw conclusive results. This may support the idea that PRP injections in the knee may be helpful in improving pain, effusion, and overall function in those with knee osteoarthritis. A similar study to this one could be conducted utilizing PRP for knee osteoarthritis rather than plantar fasciopathy to yield further informative results (Singh et al., 2017). The design was considered very appropriate at level A+ when evaluated by the CAT Manager App. The effect size and confidence interval were not reported, which is a limitation of this article. The trustworthiness of this article is still very high at 95%. This systematic review is of very high quality based upon the CAT App appraisal.

A systematic review and meta-analysis by Shen et al. (2017) studied the temporary effect of platelet-rich plasma on pain and the physical function limitations caused by knee osteoarthritis. Due to the increasing number of randomized controlled trials conducted regarding PRP injections, this study aims to review these and determine the efficacy on knee pain and function in patients with knee osteoarthritis. Randomized controlled trials that studied the

efficacy and/or safety of PRP, had human subjects, and focused on osteoarthritis of the knee were included. Studies also needed to include patients 18 years of age and older with symptomatic knee osteoarthritis and include at least 1 control group who was treated with another intra-articular agent. PRP used in combination with another treatment and studies with only published abstracts were excluded. A search was performed using Pubmed, Embase, Cochrane library, and Scopus from July 2016 through November 2016. The words "platelet", "plasma", "knee", "tibiofemoral", "patellofemoral", "arthritis", "arthritic", "cartilage", "arthrosis", and "gonarthrosis" were used in these searches. Resulting literature was reviewed and data was extracted using a data extraction table. A total of 14 randomized controlled trials were included with 1423 patients with a range of 12 to 96 participants included in PRP groups and 11 to 96 in the control groups. It should be noted that this study reported that, upon assessment, 10 articles had a high risk of bias and 4 had a moderate risk. Overall, results showed that PRP injections reduced WOMAC pain and functional scores significantly at the 3,6, and 12 months follow-up (Shen et al., 2017). The design is very appropriate at level A+ when evaluated by the CAT Manager App and was rated 95% trustworthy. There is no reported effect size and therefore it is difficult to assess precision.

In a systematic review by Laudy et al. (2014), it was pointed out that the use of PRP as a treatment method for knee osteoarthritis is still a controversial topic. This study aims to investigate the efficacy of PRP through systematic review and meta-analysis of recent research. Studies considered included randomized controlled or non-randomized controlled clinical trials with available full-text. All patients were at least 18 years old with a diagnosis of knee osteoarthritis. Studies focused on injections of PRP, or similar products, with a control group. A search of Medline, Embase, CINAHL, Web of Science, and the Cochrane library was performed.

All selected studies containing key words relating to the topic of this study were screened and data extraction then occurred. Finally, all articles chosen were assessed for quality and level of evidence. A total of 10 articles were chosen to be included. It was concluded that PRP injections were more effective for reduction of knee pain due to osteoarthritis. Of these, when compared with a placebo as the control group, PRP was comparable at the 6-month follow up post-injection. There was statistical significance found in support of PRP versus hyaluronic acid as the control group. It should be noted that this study reported that many of the included articles had a high risk of bias upon assessment for quality of evidence (Laudy et al., 2014). The design is very appropriate at level A+ when evaluated by the CAT Manager App and rated 95% trustworthy. There is no reported effect size and therefore it is difficult to assess precision.

In a randomized controlled trial conducted by Smith et al. (2016), the goal was to determine the efficacy and safety regarding PRP injections as a treatment option for knee osteoarthritis. This study is FDA-sanctioned and also utilized a double-blinded, placebo-controlled method. Patient selection was conducted by screening patients who sought care for knee pain due to osteoarthritis. Patients were included if they were 30-80 years old, had documented OA for at least 6 weeks, had continued symptoms despite other treatments, and a WOMAC score of at least 8/20. After screening 114 patients, 30 were included in the study and were randomly placed into one of two groups. Each patient was given an injection of either autologous conditioned plasma (ACP) injection or a placebo injection every week for 3 weeks. They then followed up at 2, 3, and 6 months following the injections and were assessed using WOMAC scores. They also had a visit at 12 months following the first treatment. WOMAC scores were decreased at 1 week and throughout the remainder of the follow up visits in the group receiving ACP injections. At the final 12-month follow up WOMAC scores had improved

by 78% in the ACP group and by only 7% in the placebo group (Smith et al., 2016). This randomized controlled trial is of high quality based upon the PEDro scale as it had 11/11 answers as “Yes”

The aim of this double-blinded study Fitzpatrick et al. (2018) is to determine how patients with gluteal tendinopathy respond to a single PRP injection versus a single corticosteroid injection as a treatment method. Selected patients were ages 18 to 80 years old and had a history of gluteal tendinopathy for at least 4 months, pain with activity, or pain while lying on the affected side. Patients were excluded if they had a full-thickness tear, previous surgery to the hip or tendon, anticoagulated, or a recent cortisone injection in the past 6 weeks, among others. Of the 228 patients screened, a total of 80 participated in the study and were randomized. One group received a glucocorticoid injection and the other received a PRP injection and both completed an identical supervised rehabilitation program. The mHHS was then completed at 2, 6, and 12 weeks. At the 2-week and 6-week mark, there were no differences in mHHS scores. However, at 12-weeks the mean mHHS score had improved in the PRP group compared to the corticosteroid group (Fitzpatrick et al., 2018). This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as “Yes” indicating that this article is of excellent quality.

A randomized prospective study by Kavadar et al. (2015) explored the effectiveness of improving pain and functions of 1, 2, or 3 PRP injections in patients with grade 3 osteoarthritis. A total of 98 patients, 15 males and 83 females, were included in this study. All had grade 3 knee osteoarthritis, were ages 40-75, and visited the clinic between May 2014 and October 2014 due to unilateral knee pain for at least 6 months. Patients were excluded from trial if they had

bilateral knee OA, were over 75 years old, participating in a physical therapy plan, had previous steroid, hyaluronic acid, or PRP injection in the last 6 months, history of trauma to the affected in the last 6 months, active infection, inflammation or tumor in the knee, a history of diabetes, cardiovascular disease, autoimmune disease, malignancies, or immunosuppression. They also may not have been using systemic corticosteroids 10 day prior to the PRP injection or NSAIDs for 5 days prior. Patients with genu varum or valgum deformity greater than 5-degree, pregnancy, or breastfeeding were also excluded. Participants were separated into 3 groups with 34 in each group. Group 1 had a single injection, Group 2 had two injections two weeks apart, and Group 3 had three injections, each two weeks apart. A physician under sterile conditions performed each PRP injection. Following each injection, all patients were instructed to flex and extend the knee to allow the PRP to spread appropriately through the joint. Each patient was also instructed to proceed with limited weight bearing and use of cold packs of 72 hours following each injection. Patients followed up 1, 3, and 6 months following treatment and were assessed using the visual analog scale for pain, the Western Ontario and McMaster Universities Arthritis Index, and the Timed-Up and Go test. The study remained double blinded since a different physician performed the follow up evaluations. In all three groups, the score of the VAS, TUG, and WOMAC were all better and statistically significant (p-value<0.001). The effectiveness of Group 1 was significantly lower than that of Group 2 and Group 3. This information indicates that multiple PRP injections may be more effective for the treatment of moderate osteoarthritis of the knee (Kavadar et al., 2015). In appraising this article using the CASP (Critical Appraisal Skills Programme) tool it was found that 10/11 questions were answered with “yes”, indicating that this article is likely trustworthy. It is difficult to apply these results to the local population, as the subjects of the study are a majority female.

In a systematic review, Filardo et al. (2013) aims to analyze available research regarding the rationale, indications, and expectations of PRP injections as a treatment for cartilage lesions and joint degeneration. To be included in this study, the in vitro, vivo preclinical and clinical study on PRP injections must be in the English language, study the effects specifically on cartilage, synovial tissue, and menisci. A total of 388 articles were reviewed and 59 met the criteria with 26 in vitro, 9 in vivo, 2 in both, and 22 clinical studies. PubMed was used to perform this systematic review using keywords including, “Plate-Rich Plasma”, “Platelet Concentrate”, “Platelet Lysate”, “Platelet Supernatant”, “Cartilage”, “Chondrocytes”, “synoviocytes”, “menisci”, “mesenchymal stem cells”. All data was reviewed from the studies and categorized based upon the type of study and then sub-type. A total of 388 articles were reviewed and 59 met the criteria with 26 in vitro, 9 in vivo, 2 in both, and 22 clinical studies. There is pre-clinical support of the use of PRP injections as a means of joint tissue healing, but there have only been a few high-quality clinical trials published showing limited improvement over time, especially in younger patients without a diagnosis of advanced knee degeneration. This information overall supports the use of PRP, especially as it may support the overall health of the joint, rather than just the cartilage as previously thought (Filardo et al., 2013). The design is very appropriate at level A+ when evaluated by the CAT Manager App and rated 95% trustworthy. There is no reported effect size of CI and therefore it is difficult to assess precision.

In a diagnostic study, Burchard et al. (2019) investigated how different levels of cartilage damage in patients with knee osteoarthritis is affected by platelet-rich plasma (PRP) injections. Patients who were at least 18 years old and had been diagnosed via MRI were considered and enrolled in the study. Subjects were excluded from this study if they lacked flexion beyond 90 degrees or lacked extension beyond 20 degrees, had a history of knee surgery, or had various

chronic diseases, such as rheumatoid arthritis, cancer, or diabetes. Prior to the start of the trial, each subject had a pre-treatment MRI that was analyzed for osteoarthritis using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) method. All subjects could not be treated with any anti-inflammatory medications during the treatment period. In order to assess how they were affected by the treatments; each subject was surveyed using the WOMAC and VAS prior to the first injection and then again at the 24-week follow-up. A total of 59 subjects participated in this study. After the pre-treatment MRI and WORMS Cartilage Score evaluations, it was found that 20.3% had mild, 55.9% had moderate, and 23.7% had severe ratings of cartilage damage possibly due to osteoarthritis. The VAS scores were compared and it was reported that they decreased following PRP by a mean of 3.58 points while the WOMAX scores decreased by a mean of 23.51 points in participants who had PRP. Through regression analysis, no relationship was found to be statistically significant ($p > 0.05$) between the level of osteoarthritis determined by the WORMS score and the response to PRP. It was reported that the female subjects' WOMAC scores decreased more than those of the male subjects. Based upon the results, it was concluded that PRP injections may aid in improving pain and quality of life in patients with knee osteoarthritis, especially in female patients. This diagnostic study speaks to the efficacy of PRP injections in patients suffering from pain and decreased quality of life due to their knee osteoarthritis. Based upon this study, PRP may be an effective treatment possibility, especially in women (Burchard et al., 2019). When evaluated by the CRAAP test, this article ranked at excellent with 46/50 overall. In currency, it scored 10/10 as it was published recently in 2019, uses current articles for support, and includes functional links within the article. It ranks at 8/10 in relevance as it only included PRP as a study topic which is only helpful for a portion of this research. In authority, it ranked 9/10 as its authors are healthcare authorities and orthopedic

physicians working in a healthcare setting in research and appear qualified to report on this topic. A 9/10 in accuracy was given and overall this article ranked at excellent with 46/50.

The systematic review explored in this analysis was authored by Sirbu et al. (2017) and studied the efficacy and uses of platelet-rich plasma (PRP) injections to the knee as a treatment for osteoarthritis. The main purpose was to provide a systematic analysis of the current literature in order to answer questions regarding the efficacy of PRP injections as a means of treatment. In October of 2013, databases including PubMed, Embase, and CINAHL were searched with the keywords “platelet-rich plasma” and “knee” and “osteoarthritis” and “platelet-rich plasma” and “knee” and “osteoarthritis”. To be included in this study, the articles needed to have an available abstract, had original data, accepted knee OA classification criteria, and discussed PRP injections as a treatment for knee OA. Through this search, 319 abstracts were reviewed and a total of 8 relevant articles included in this systematic review. There were 4 prospective observational studies, 2 randomized controlled trials, and 2 comparative studies of PRP and hyaluronic acid. It was then concluded that PRP injections might be a good treatment option for knee osteoarthritis. However, the study reported that most included studies were ultimately inconclusive due to small sample size. Further research on a larger scale is necessary to determine if PRP is a useful treatment for knee osteoarthritis (Sirbu et al., 2017). The design is appropriate at level B when evaluated by the CAT Manager app. Limitations of this article include the high likelihood that pertinent studies were not included and the process of extracting data and evaluating data was not reported. Neither the effect size nor the Confidence Interval (CI) was included.

In a quasi-experimental time series analysis, conducted by H. Sucuglu in 2019, the short-term efficacy of platelet-rich plasma injections to the knee in patients with pain due to

osteoarthritis were studied. Participants included patients of the Physical Therapy and Rehabilitation clinic of the Private Bagcilar Aktif Medicine Center and were committed to following up as outpatients and as voluntary subjects. It was also used at the 12-week follow-up. Each patient included was between 40 and 80 years old, had chronic knee pain for at least 3 months, and had been diagnosed with osteoarthritis according to the American College of Rheumatology standards and diagnosed by x-ray as grades 2-4 according to the Kellgren and Lawrence grading system. Subjects were excluded from the study if they had knee instability, a history of trauma, had an active infection, were pregnant, used anticoagulants or NSAIDs 5 days prior to PRP injection, had a corticosteroid injection to the knee less than 6 months ago, or had systemic disease or disorder. Each participant had a total of 3 PRP injections to the affected knee once every other week. The VAS was used on the day of the first injection, the second injection at week 3, and then at the third injection at week 6. Initially, 76 patients were examined, but a total of 69 patients remained following exclusion criteria elimination. During the treatment process, another 27 patients were lost due to lack of follow-up, following either the first, second, or third injection. Statistical analysis was performed and it was found that VAS scores at rest improved 2.53 points and 3.93 points with activity when comparing day 0 scores to week 12 scores. The greatest improvement in VAS scores seemed to occur between week 6 and week 12. This was found to have a p-value less than 0.05 indicating its statistical significance. It is important to note that there was greater improvement in the patients with only grade II osteoarthritis compared to the patients who had grades 3-4 arthritis on the Kellgren-Lawrence scale. This study provides additional support in answering the proposed clinical question. It provides evidence of pain improvements due to PRP, especially in patients with earlier state osteoarthritis of the knee. It also calls attention to the importance of having a control group in a

study of this sort. Due to the lack of a control group, it is difficult to rule out the placebo effect in many of the patients and this should be considered when evaluating this article for significance in regard to using PRP as an effective treatment (Sucuglu, 2019). The design is moderately appropriate at a level B when evaluated by the CAT Manager app. Limitations of this article include that the intervention was not completely independent to outside changes over time and that only 42 of the original 69 patients remained in the study at the end, indicating a dropout rate greater than 20%. The effect size and CI were also not reported in this study. Therefore, it is indicated that the trustworthiness of this article is only 70%.

Strengths and Weaknesses

The studied articles include: randomized controlled trials, systematic reviews, meta-analyses, prospective randomized studies, a diagnostic study, and a quasi-experimental times series study. The order in which the articles are discussed is strategic in that they are arranged by quality and relevance of information provided for the purpose of this study. A key strength of this research is the large number of high quality randomized controlled trials and systematic reviews that are included in support. For instance, studies conducted by Jubert et al. (2017) and Malahias et al. (2018) are of high quality and study PRP injections versus corticosteroid steroid injections. However, it should be noted that the article by Malahias et al. (2018) focuses on these different injections in the context of trapeziometacarpal arthritis rather than osteoarthritis of the knee joint. Ben-Nafa et al. (2018), Singh et al. (2017), and Fitzpatrick et al. (2018) encountered a similar scenario with the topic of lateral epicondylitis, plantar fasciopathy, and gluteal tendinopathy respectively, rather than knee osteoarthritis. The information should still be valued though, as it is high quality data regarding these differing treatment options for musculoskeletal

injuries. The articles by Ben-Nafa et al. (2018), Maricar et al. (2012), and Singh et al. (2017), were all systematic reviews, which were appraised highly by the CAT manager app. Although they may have smaller sample sizes, the selection criteria were specific and made sense for each of individual criteria for the research. The article by Burchard et al. (2019) was a diagnostic study appraised highly by the CRAAP tool. However, it should be noted that the CRAAP tool might not be completely subjective in its questions so further appraisal may be necessary. While the systematic reviews and meta-analyses conducted by Shen et al. (2017) and Laudy et al. (2014) were rated with highly by the CAT Manager App and contain valued information regarding the efficacy and function of PRP, they had no reported effect size and therefore it is difficult to assess them for precision in their results.

Among the articles in this research, there is a pattern that PRP is more effective in the long term than corticosteroid injections, especially in patients in the early stages of knee osteoarthritis. This is evident in the articles by Nabi et al. (2018), Malahias et al. (2018), Ben-Nafa et al. (2018), Huang et al. (2019), Shen et al. (2017), Smith et al. (2016), and Fitzpatrick et al. (2018). However, a limitation to note with these articles is that they do not all compare PRP injections to corticosteroid injections. Some compare to another injury and some study only PRP injections or only corticosteroid injections. It is important to consider the results of these studies as well as they are well conducted and speak to the effectiveness of these injections as a viable treatment option.

Another weakness to note is the low sample sizes along with a lack of double-blinded studies in the included articles, especially in the randomized controlled trials. This is an area to be noted when considering future research. Ideally, to ensure a lack of bias and consistency of

results, a large sample size should be used and both researchers and subjects should be blinded to the treatment they are given. However, it should be noted that this is not always possible due to ethical issues regarding informed consent of the subjects.

Summary

In conclusion, the matrix serves the purpose of allowing for easy identification of articles along with a summary of what each article covers and what it means for the use of PRP versus corticosteroid injections in patients with knee osteoarthritis. A total 17 of articles are included which include six randomized controlled trials, four systematic reviews, 3 systematic reviews and meta-analyses, two prospective randomized studies, one diagnostic study, and one quasi-experimental time series analysis. All were appraised using the appropriate tools and assessed for inclusion in the recommendations given through this research. It is noteworthy that not all appraisal tools are completely objective. Rather than simple “yes” or “no” answers, tools such as CRAAP and CASP use subjective questions and rely on the appraiser to provide scoring, rather than a predetermined system. This should be considered when determining the trustworthiness of the article as assessment tools that are completely objective would be preferred. It was found that most systematic reviews were highly trustworthy given the high number of randomized controlled trials that they included, but most suffered from a low sample size considering the results. Low sample sizes and lack of double blinding were also noted in some of the randomized controlled trials that were included.

In the next chapter, the results will be further discussed and their implications in the athletic training setting will be explained. The question of how corticosteroid injections compare with PRP injections in improving symptoms of pain and effusion of the knee in patients with

osteoarthritis of the knee will continue to be explored. This will be done through identification of current trends and areas lacking in the literature along with recommendations for future research.

Chapter 4 – Discussion, Implications, and Conclusions

Trends and Gaps of the Literature

The search methodology used for this project provided the greatest results when using "corticosteroid" in conjunction with other keywords. For example, when searching Google Scholar, "corticosteroid injections in knee osteoarthritis" yielded about 18,100 results and another search using "PRP injections in knee arthritis yielded only about 9,270 results. The phrase "hyaluronic acid injections versus corticosteroid in knee osteoarthritis" showed about 11,300 results, while "PRP injections versus corticosteroid in knee osteoarthritis" only showed about 5,020 results. When "injection" "PRP", "hyaluronic acid" and "corticosteroid" were searched in conjunction with "efficacy", there were about 17,300 results, 36,600 results, and 17,500 results, respectively. A similar strategy was used with PubMed and CLIC, which then yielded similar results. This points to the gap in literature regarding the efficacy of reducing pain, effusion, and even function of the knee joint in patients with knee osteoarthritis who have received a PRP injection as treatment. There have been many studies conducted on PRP, hyaluronic acid, and corticosteroid injections to investigate their efficacy, but there have been significantly more conducted regarding hyaluronic acid. However, there was a smaller selection of articles found regarding hyaluronic acid compared to PRP. Thus, the reasoning for the elimination of hyaluronic acid as an injection investigated in this project. There seems to be another gap regarding PRP injections specifically for knee arthritis, therefore in this study PRP injections used to treat ailments such as lateral epicondylitis, plantar fasciopathy, among others were considered.

In addition to the lack of research regarding PRP in relation to knee osteoarthritis and PRP versus corticosteroid injections, there was a larger number of systematic reviews and meta-analyses found and used in this project. This is reflected in the matrix as many of the included articles are of this type. It should also be noted that four of the included seventeen articles are findings based upon PRP injections used as a treatment for other musculoskeletal conditions. While these articles are highly regarded in this research, this limitation should be considered when utilizing the information for decisions concerning osteoarthritis of the knee. Based upon this knowledge, it would be recommended that future research consider these topics through other means, especially by a double-blinded randomized controlled trial, and should focus on how PRP injections and corticosteroid injections effect patients with knee osteoarthritis.

Major Findings and Implications

In considering how corticosteroid injections compare with PRP injections in improving symptoms of pain and effusion in patients with knee osteoarthritis, a major finding among currently published articles was noted.

The major finding that was seen among the articles was that PRP injections tend to better relieve pain and function of the knee in patients within the early stages of osteoarthritis and when used as a long-term treatment when compared to corticosteroid injections. This was evident in articles by Nabi et al. (2018), Malahias et al. (2018), Ben-Nafa et al. (2018), Huang et al. (2019), Shen et al. (2017), Smith et al. (2016), and Fitzpatrick et al. (2018). While this conclusion was also reached in the article by Jubert et al. (2017), the conclusion was not found to be statistically significant. This conclusion was refuted in the article published by Singh et al. (2017) in finding no differences in results between PRP injections and corticosteroid injections in a long-term follow up. However, it should be noted that the study by Burchard et al. (2019) is a diagnostic

study and is not the optimal source of data, as a randomized controlled trial or a systematic review may be. It should also be noted that studies by Malahias et al. (2018), Ben-Nafa et al. (2018), Singh et al. (2017), and Fitzpatrick et al. (2018) were regarding trapeziometacarpal arthritis, lateral epicondylitis, plantar fasciopathy, and gluteal tendinopathy respectively, rather than knee osteoarthritis. However, they should remain tangible evidence due to the similar mechanism of healing associated with PRP injections.

Based upon this finding, implications for the athletic training practice may involve discussing the proper use of PRP injections with other healthcare providers and establishing best practice standards. When discussing the options for treatment of osteoarthritis of the knee, it is important to consider these studies and those presented in this research to the physician or healthcare provider, along with the patient to make the best possible decision for the patient. An athletic trainer has the unique opportunity to have an open and informational discussion with the provider as well as advocate for the patient. Discussing whether to proceed with a PRP injection or a corticosteroid injection would be an opportune time to put this information into practice. In another sense, the major conclusion of this project can be a starting point for further research regarding the efficacy of PRP injections in the context of knee osteoarthritis. A better understanding of these injections may then lead to better evidence and best practice standards, so that health insurance companies might begin to cover more treatment options, such as PRP injections (Jones, 2018). Since the diagnosis of arthritis is projected to continue to grow and reach as many as 78 million people by 2040, now is the time to grow in knowledge surrounding possible treatments for osteoarthritis of the knee (Centers for Disease Control and Prevention, 2018).

Conclusion

Osteoarthritis is a joint disease that may be associated with long-term side effects and can be debilitating depending on severity. As the knees and hips are the greatest weight bearing joints in the body, osteoarthritis of these joints tends to be the most burdensome (Litwic et al., 2013). In recent years, there has been a greater focus in research on developing alternative treatments for osteoarthritis of the knee due to its growing significance in society. According to the Centers for Disease Control and Prevention, there were about 54.4 million adults in the United States with an arthritis diagnosis from 2013-2015. This number includes those with forms of all arthritis, such as rheumatoid arthritis, gout, lupus, or fibromyalgia. It is estimated that there will be a total of about 78 million people diagnosed with arthritis by 2040 (Centers for Disease Control and Prevention, 2018).

This project considers the question: How do corticosteroid injections compare with platelet-rich plasma (PRP) injections in improving symptoms of pain and effusion of the knee in patients with osteoarthritis of the knee? In researching this question, a total of seventeen articles were selected to include in the study based upon the stated inclusion and exclusion criteria. Common trends in the literature showed that PRP tends to have longer-lasting effects when compared to corticosteroid injections in patients with knee osteoarthritis. This conclusion was formed from six randomized controlled trials, four systematic reviews, three systematic reviews and meta-analyses, two prospective randomized studies, one diagnostic study, and one quasi-experimental time series analysis. All were appraised using the appropriate tools and assessed for inclusion in the recommendations given through this research. In the future, it is recommended that further research be conducted regarding the topics of the effects of PRP injections on knee

osteoarthritis and the efficacy of PRP injections versus corticosteroid injections in patients with knee osteoarthritis.

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Appendix A: Matrix of the Literature

Source: Jubert, N. J., Rodríguez, L., Reverté-Vinaixa, M. M., & Navarro, A. (2017). Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. *Orthopaedic Journal of Sports Medicine,5*(2), 232596711668938. doi:10.1177/2325967116689386

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: The purpose of this study is to determine the effectiveness of platelet-rich plasma (PRP) injections in the advanced stages of knee osteoarthritis. **Method:** Randomized Controlled Trial	Subjects were current patients on a wait list for a total knee arthroplasty with a diagnosis of osteoarthritis. A total of 75 patients were enrolled in the study. Subjects were randomly assigned to either the PRP intervention group or the control group which received betamethasone and bupivacaine. All patients were blinded to the treatment they received.	Each group either received PRP or the control (betamethasone and bupivacaine) injection to the medial compartment of the symptomatic knee. Syringes were opaque and the same person performed all injections to decrease bias and keep the double double-blinded. Patients were reevaluated at one, three, and six weeks post injection. Patients were evaluated using a visual analog scale, Knee Injury and Osteoarthritis Outcome Score, and Short Form-36 to evaluate for quality of life.	There was a decrease in VAS scores in both the control and PRP groups, but when compared to baseline there was no statistical significance. The KOOS outcome score differences in the PRP group were greater in each area, but they were still not statistically significant. The SF-36 scores at 6 months were greater in the PRP group when compared to baseline scores.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as "Yes" indicating that this article is of excellent quality.			

Source: Nabi, B. N., Sedighinejad, A., Mardani-Kivi, M., Haghighi, M., Roushan, Z. A., Tehran, S. G., & Biazar, G. (2018). Comparing the Effectiveness of Intra-articular Platelet-Rich Plasma and Corticosteroid Injection under Ultrasound Guidance on Pain Control of Knee Osteoarthritis. *Iranian Red Crescent Medical Journal*, *20*(3). doi: 10.5812/ircmj.62157

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: The aim of this study is to evaluate how PRP injections and corticosteroid injections compare in effectiveness to control pain in patients with knee osteoarthritis. **Method:** Randomized controlled trial	Patients included in this study had grades II-III knee osteoarthritis and were seen in the Guilan University of Medical Sciences from April 2016 through June 2017. Patients were included if they were 20-75 years old, had diagnosed grades II-III knee osteoarthritis, and had knee pain for at least 3 months without improvement from other interventions. Patients were excluded if they had knee joint defomityies, cancer, rheumatoid arthritis, BMI greater than 35 kg/m^2, pregnant or breastfeeding, infection, blood abnormalities or disorders, among other chronic conditions.	A total of 67 patients participated in this study. They were sorted randomly into either the triamcinolone group or the PRP group. Each participant received their injection under ultrasound once per month for 3 months. Then pain was evaluated using the Visual Analog Scale (VAS) and the Knee injury and Osteoarthritis Outcome Score (KOOS) each month for 3 months and then 6 months following the conclusion of the treatment.	There were lower scores in pain on VAS in the PRP group compared to the triamcinolone group. Statistically significant (p=0.385) results were found at 2, 3, and 6 months follow ups. There was also improved quality of life, functions of daily living, and overall improved symptoms.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 8/11 answers as "Yes" indicating that this article is of good quality. Weaknesses of this study included lack of concealed allocation and lack of blinding due to ethical reasons in treatments given.			

Source: Malahias, M.-A., Roumeliotis, L., Nikolaou, V. S., Chronopoulos, E., Sourlas, I., & Babis, G. C. (2018). Platelet-Rich Plasma versus Corticosteroid Intra-Articular Injections for the Treatment of Trapeziometacarpal Arthritis: A Prospective Randomized Controlled Clinical Trial. *Cartilage*, 194760351880523. doi: 10.1177/1947603518805230

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: There have been systematic reviews conducted which indicate symptomatic relief of knee osteoarthritis with PRP injections. This study aims to investigate the efficacy of PRP in providing relief of	This study began with 48 patients who all had grades I-III osteoarthritis of the first CMC joint and had been examined between July 2012 and December 2014. Patients were excluded if they had rheumatic disease, comorbidities of the	After elimination due to exclusion criteria, there were 33 patients who remained to participate in the study. Informed consent was signed by each participant and each was then randomly assigned to one of the two groups. One group	In comparison with the corticosteroid injection, the group who had the PRP injection had statistically significantly better improvement of their VAS scores (p=0.015) and Q-DASH scores (p=0.025). It was concluded that corticosteroids

symptoms in patients with trapeziometacarpal arthritis. **Method:** Randomized controlled trial	hand, history of gout, previous surgery to the affected hand, or an injection in the last 12 months.	received 2 ultrasound guided PRP injections, 2 minutes apart, while the other group received 2 ultrasound guided injections, 15 minutes apart, of methylprednisolone and lidocaine. Each patient then followed up at 3 months and 12 months and were evaluated based upon the visual analogue scale (VAS), and the Q-DASH. Both the patient and the physician during evaluation were blinded.	offer better short-term relief, but PRP injections may be the better treatment option for long term relief.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 10/11 answers as "Yes" indicating that this article is of good quality. Weaknesses of this study included lack of blinding of all subjects.			

Source: Maricar, N., Callaghan, M. J., Felson, D. T., & Oneill, T. W. (2012). Predictors of response to intra-articular steroid injections in knee osteoarthritis--a systematic review. *Rheumatology,52*(6), 1022-1032. doi:10.1093/rheumatology/kes368

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: The purpose of this study is to determine the factors that determine the response to an intra-articular steroid injection in patients with knee osteoarthritis. **Method:** Systematic Review	Studies that utilized adults with osteoarthritis of the knee proven by ACR criteria or diagnosed by radiographs. Both experimental studies and observational studies were included.	Information from each article used was presented in a table to determine each article's common predictors and then classified as statistically significant, null, or not statistically significant.	A total of 11 of the 696 retrieved articles fully met inclusion criteria and were reviewed. Predictors identified include, effusion, aspiration, absence of synovitis, injection with ultrasound guidance, structural severity of disease, and pain.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The effect size and confidence interval are not reported, which is a weakness of this article. The trustworthiness of this article is still very high at 95%. This systematic review is of very high quality based upon the CAT Appappraisal.			

Source: Ben-Nafa, W., & Munro, W. (2018). The effect of corticosteroid versus platelet-rich plasma injection therapies for the management of lateral epicondylitis: A systematic review. *Sicot-J*, *4*, 11. doi: 10.1051/sicotj/2017062

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: This study seeks to identify the effects of corticosteroid injections versus PRP injections on patients with lateral epicondylitis. **Method:** Systematic Review	From a narrowed down search, a total of 43 articles were found and considered. After review, 5 randomized controlled trials were included after exclusions including articles not written in English or were published prior to 2005. Articles including patients with elbow pain other than lateral epicondylitis and patients who had other injections were also excluded.	There were 11 databases searched to find about 732 articles. These articles were sorted and excluded if needed by looking for relevance, references, and type of research conducted. All data was assessed prior to evaluation of the quality of the article.	Search results showed 732 qualifying papers. 43 remained when exclusions for duplications, review articles, and conference papers were applied. These included 5 randomized controlled trials with 250 participants. Through these articles, it was concluded that corticosteroid injections provided more rapid symptomatic relief when compared to PRP injections. However, patients who had PRP had greater tendon thickness. Both patients who had corticosteroid injections or PRP injections had reduced point tenderness of the common extensor tendon.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The design was very appropriate and it was concluded that this article is 95% trustworthy. There is no reported effect size of CI and therefore it is difficult to assess precision.			

Source: Huang, Y., Liu, X., Xu, X., & Liu, J. (2019). Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis. *Der Orthopäde*, *48*(3), 239–247. doi: 10.1007/s00132-018-03659-5

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: The purpose of this study is to determine the effectiveness of corticosteroid injections, platelet-rich plasma injections, and hyaluronic acid	Patients with grades 1-2 arthritis confirmed with radiographs, ages 40-65, BMI < 30, and had stable knees were included. There were a total of 120 that	Outcomes were assessed using the WOMAC scale and VAS completed prior to the first injection and then every 3 months. Each injection was	When compared to pre-treatment scores on the WOMAC and VAS, there was significant improvement in both. The most improvement was noted within

injections and whether one is superior to another. **Method:** Prospective, randomized study	met these inclusion criteria. These patients were randomized into 3 groups, 1 for each type of injection.	administered in its appropriate fashion, in the same room, by the same people.	the first 3 months for all groups. PRP injections seemed to greater improvement than the scores of the HA and CS groups.
Assessment: In appraising this article using the CASP (Critical Appraisal Skills Programme) tool it was found that 10/11 questions were answered with "yes", indicating that this article is likely trustworthy. The remaining questions were able to be answered with evidence from the article.			

Source: Duif, C., Vogel, T., Topcuoglu, F., Spyrou, G., Pellengahr, C. V. S., & Lahner, M. (2015). Does intraoperative application of leukocyte-poor platelet-rich plasma during arthroscopy for knee degeneration affect postoperative pain, function and quality of life? A 12-month randomized controlled double-blind trial. *Archives of Orthopaedic and Trauma Surgery*, *135*(7), 971–977. doi: 10.1007/s00402-015-2227-5

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: This double-blinded study aims to investigate how leukocyte-poor PRP affects degenerative lesions and symptoms in knee osteoarthritis when injected during knee arthroscopy. **Method:** Randomized controlled trial	Patients who were seen between January 2010 and December 2011 who had non-traumatic knee pain, image diagnosed osteoarthritis of the knee, and has failed conservative treatment after 12 weeks and is now considering arthroscopic surgical intervention. Patients were excluded if they were unable to provide informed consent, if they had circumscribed chondral damage, infection, rheumatological disorders, corticosteroid injection within the last 3 months, collateral ligament instability greater than grade II, immunosuppression, cancer, or other serios conditions. A total of 58 patients were chosen for this study with 24 in the PRP group and 34 in the control group.	All patients had knee arthroscopy performed and after interventions were completed, depending on the assigned group, the patient was given either the placebo or PRP injection. All patients were closed in the same protocol and were allowed to fully weight bear immediately. Double blinding was used to ensure by doctors as each followed the same follow-up procedure for both groups. Pain, function, and quality of life were assessed at baseline, 6-week, 6-month, and 12-month follow up using the Visual Analog Scale (VAS) and SF-36.	A total 5 patients were lost to follow-up, leaving 91.4% of patients who initially were enrolled in the study. At the 6-month follow up, pain was lower in the PRP group (p-value=0.008). However, at the 12 month follow up the control group had low scores of pain (p-value=0.063). It should also be noted that the quality of life in the PRP group at 6-weeks and 6-months was significantly higher than that of the control group, but this was equal between the groups at the 12-month follow up. From this information, it can be concluded that intraoperative application of PRP, specifically leukocyte-poor PRP, may improve pain and knee unction within the 6-12 month span following the treatment when compared to interventions with only arthroscopy.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as "Yes" indicating that this article is of excellent quality.			

Source: Singh, P., Madanipour, S., Bhamra, J. S., & Gill, I. (2017). A systematic review and meta-analysis of platelet-rich plasma versus corticosteroid injections for plantar fasciopathy. *International Orthopaedics*, *41*(6), 1169–1181. doi: 10.1007/s00264-017-3470-x

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: To determine whether platelet-rich plasma injections provide better pain relief in patients with plantar fasciopathy compared to corticosteroid injections. **Method:** Systematic review and meta-analysis	A total of 10 studies were included following database search and application of inclusion and exclusion criteria. Studies were included if they fit the purpose of the study, were a randomized controlled trial, prospective study, observational study, or a retrospective study. They were also included if they reported data on at least one quality of life or pain score. Patients also needed to have no previous surgical history for plantar fasciopathy. All studies required at least 10 subjects participating.	Ovid database, EMBASE, and MEDLINE were used to search with the terms "platelet-rich plasma", "PRP", "plantar fasciitis", "plantar fasciopathy", "corticosteroids", "steroids", "injection", "visual analogue score", and "quality of life". All resulting articles were investigated for inclusion and exclusion criteria. All articles were limited to between January 2000 and September 2016. There were no limits set for language.	The 10 studies that were included were reviewed. It was concluded that at the subject's 3-month follow up, those who had PRP injections had improved VAS scores, but at the 6-month follow up there was no difference in the improvement of VAS scored between PRP and corticosteroid injections.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The effect size and confidence interval are not reported, which is a weakness of this article. The trustworthiness of this article is still very high at 95%. This systematic review is of very high quality based upon the CAT Appappraisal.			

Source: Shen, L., Yuan, T., Chen, S., Xie, X., & Zhang, C. (2017). The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *Journal of Orthopaedic Surgery and Research*, *12*(1). doi: 10.1186/s13018-017-0521-3			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Purpose: Due to the increasing number of randomized controlled trials conducted regarding PRP injections, this study aims to review these and determine the efficacy on knee pain and function in patients with knee osteoarthritis. **Method:** Systematic review and meta-analysis	Randomized controlled trials that studied the efficacy and/or safety of PRP, had human subjects, and focused on osteoarthritis of the knee were included. Studies also needed to include patients 18 years of age and older with symptomatic knee osteoarthritis and include at least 1 control group who was treated with another intra-articular agent. PRP used in combination with another treatment and studies with only published abstracts were excluded.	A search was performed using Pubmed, Embase, Cochrane library, and Scopus from July 2016 through November 2016. The words "platelet", "plasma", "knee", "tibiofemoral", "patellofemoral", "arthritis", "arthritic", "cartilage", "arthrosis", and "gonarthrosis" were used in these searches. Resulting literature was reviewed and data was extracted using a data extraction table.	A total of 14 randomized controlled trials were included with 1423 patients with a range of 12 to 96 participants included in PRP groups and 11 to 96 in the control groups. It should be noted that upon assessment 10 articles had a high risk of bias and 4 had a moderate risk. Overall, results showed that PRP injections reduced WOMAC pain and functional scores significantly at the 3,6, and 12 months follow-up.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The design was very appropriate and it was concluded that this article is 95% trustworthy. There is no reported effect size and therefore it is difficult to assess precision.			

Source: Laudy, A. B. M., Bakker, E. W. P., Rekers, M., & Moen, M. H. (2014). Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *British Journal of Sports Medicine*, *49*(10), 657–672. doi: 10.1136/bjsports-2014-094036			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Purpose: As the use of PRP as a treatment method for knee osteoarthritis is still a controversial topic, this study aims to investigate the efficacy of PRP through systematic review and meta-analysis of recent research. **Method:** Systematic review and meta-analysis	Studies considered included randomized controlled or non-randomized controlled clinical trials with available full-text. All patients were at least 18 years old with a diagnosis of knee osteoarthritis. Studies focused on injections of PRP, or similar products, with a control group.	A search of Medline, Embase, CINAHL, Web of Science, and the Cochrane library was performed. All selected studies containing key words relating to the topic of this study were screened and data extraction then occurred. Finally, all articles chosen were assessed for quality and level of evidence.	A total of 10 articles were chosen to be included. It was concluded through analysis that PRP injections were more effective for reduction of knee pain due to osteoarthritis. Of these, when compared with a placebo as the control group, PRP was comparable at the 6-month follow up post-injection. There was statistical significance found in support of PRP versus hyaluronic acid as the control group. It should be noted that most articles included had a high risk of bias upon assessment for quality of evidence.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The design was very appropriate and it was concluded that this article is 95% trustworthy. There is no reported effect size and therefore it is difficult to assess precision.			

Source: Smith, P. A. (2016). Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis. *The American Journal of Sports Medicine*, *44*(4), 884–891. doi: 10.1177/0363546515624678			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Purpose: The aim of this study is to determine the efficacy and safety regarding PRP injections as a treatment option for knee osteoarthritis. This study is FDA-sanctioned and also utilized a double-blinded, placebo-controlled method. **Method:** Randomized controlled trial	Patient selection was conducted by screening patients who sought care for knee pain due to osteoarthritis. Patients were included if they were 30-80 years old, had documental OA for at least 6 weeks, had continued symptoms despite other treatments, and a WOMAC score of at least 8/20.	After screening 114 patients, 30 were included in the study and were randomly placed into one of two groups. Each patient was given an injection of either autologous conditioned plasma (ACP) injection or a placebo injection every week for 3 weeks. They then followed up at 2, 3, and 6 months following the injections and were assessed using WOMAC scores. They also had a visit at 12 months following the first treatment.	WOMAC scores were found to be decreased at 1 week and throughout the remainder of the follow up visits in the group receiving ACP injections. At the final 12-month follow up WOMAC scores had improved by 78% in the ACP group and by only 7% in the placebo group.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as "Yes" indicating that this article is of excellent quality.			

Source: Fitzpatrick, J., & O'Donnell, J. (2018). The Effectiveness of Platelet-Rich Plasma Injections in Gluteal Tendinopathy: Response. *The American Journal of Sports Medicine*, *46*(8). doi: 10.1177/0363546518773719			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**

Purpose: The aim of this double-blinded study is to determine how patients with gluteal tendinopathy responds to a single platelet rich plasma injection versus a single corticosteroid injection as a treatment method. **Method:** Randomized controlled trial	Selected patients were ages 18 to 80 years old and had a history of gluteal tendinopathy for at least 4 months, pain with activity, or pain while laying on the affected side. Patients were excluded if they had a full-thickness tear, previous surgery to the hip or tendon, anticoagulated, or a recent cortisone injection in the past 6 weeks, among others.	Of the 228 patients screen, a total of 80 participated in the study and were randomized. One group received a glucocorticoid injection and the other received a PRP injection and both completed an identical supervised rehabilitation program. The mHHS was then completed at 2, 6, and 12 weeks.	At the 2-week and 6-week mark, there were no differences in mHHS scores. However, at 12-weeks the mean mHHS score had improved in the PRP group compared to the corticosteroid group.
Assessment: This randomized controlled trial is of high quality based upon the PEDro scale. This study had 11/11 answers as "Yes" indicating that this article is of excellent quality.			

Source: Kavadar, G., Demircioglu, D. T., Celik, M. Y., & Emre, T. Y. (2015). Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: a randomized prospective study. *Journal of Physical Therapy Science*, *27*(12), 3863–3867. doi: 10.1589/jpts.27.3863

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: This study aimed to determine the effectiveness of improving pain and functions of 1, 2, or 3 PRP injections in patients with grade 3 osteoarthritis. **Method:** Randomized prospective study	A total of 98 patients, 15 males and 83 females, were included in this study. All had grade 3 knee osteoarthritis, were ages 40-75, and visited the clinic between May 2014 and October 2014 due to unilateral knee pain for at least 6 months. Patients were excluded from trial if they had bilateral knee OA, were over 75 years old, participating in a physical therapy plan, had previous steroid, hyaluronic acid, or PRP injection in the last 6 months, history of trauma to the affected in the last 6 months, active infection, inflammation or tumor in the knee, a history of diabetes, cardiovascular disease, autoimmune disease, malignancies, or immunosuppression. They also may not have been using systemic corticosteroids 10 day prior to the PRP injection or NSAIDs for 5 days prior. Patients with genu varum or valgum deformity greater than 5 degree, pregnancy, or breastfeeding were also excluded.	Participants were separated into 3 groups with 34 in each group. Group 1 had a single injection, Group 2 had two injections two weeks apart, and Group 3 had three injections, each two weeks apart. Each PRP injection was performed by a physician under sterile conditions. Following each injection, all patients were instructed to flex and extend the knee to allow the PRP to spread appropriately through the joint. Each patient was also instructed to proceed with limited weight bearing and use of cold packs of 72 hours following each injection. Patients followed up 1, 3, and 6 months following treatment and were assessed using the visual analog scale for pain, the Western Ontario and McMaster Universities Arthritis Index, and the Timed-Up and Go test. The study remained double blinded since a different physician performed the follow up evaluations.	There were 98 patients who completed the entire study, 15 males and 83 females. In all three groups, the score of the VAS, TUG, and WOMAC were all better and statistically significant (p-value<0.001). The effectiveness of Group 1 was significantly lower than that of Group 2 and Group 3. This information indicates that multiple PRP injections may be more effective for the treatment of moderate osteoarthritis of the knee.
Assessment: In appraising this article using the CASP (Critical Appraisal Skills Programme) tool it was found that 10/11 questions were answered with "yes", indicating that this article is likely trustworthy. It is difficult to apply these results to the local population, as the subjects of the study are a majority female.			

Source: Filardo, G., Kon, E., Roffi, A., Matteo, B. D., Merli, M. L., & Marcacci, M. (2013). Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surgery, Sports Traumatology, Arthroscopy*, *23*(9), 2459–2474. doi: 10.1007/s00167-013-2743-1

Design/Purpose	Sample/Setting	Design Instruments	Results
Purpose: This study aims to analyze available research regarding the rationale, indications, and expectations of PRP injections as a treatment for cartilage lesions and joint degeneration. **Method:** Systematic Review	To be included in this study, the in vitro, vivo preclinical and clinical studied on PRP injections must be in the English language, study the effects specifically on cartilage, synovial tissue, and menisci. A total of 388 articles were reviewed and 59 met the criteria with 26 in vitro, 9 in vivo, 2 in both, and 22 clinical studies.	PubMed was used to perform this systematic review using keywords including, "Plate-Rich Plasma", "Platelet Concentrate", "Platelet Lysate", "Platelet Supernatant", "Cartilage", "Chondrocytes", "synoviocytes", "menisci", "mesenchymal stem cells". All data was reviewed from the studies and categorized based	A total of 388 articles were reviewed and 59 met the criteria with 26 in vitro, 9 in vivo, 2 in both, and 22 clinical studies. There have been an increasing number of articles published over time regarding this topic. There is pre-clinical support of the use of PRP injections as a means of joint tissue healing, but there have only been a few high-quality clinical trials published

		upon the type of study and then sub-type.	showing limited improvement over time, especially in younger patients without a diagnosis of advanced knee degeneration. This information overall supports the use of PRP especially as it may support the overall health of the joint, rather than just the cartilage as previously thought.
Assessment: The design is very appropriate at level A+ when evaluated by the CAT Manager app. The design was very appropriate and it was concluded that this article is 95% trustworthy. There is no reported effect size of CI and therefore it is difficult to assess precision.			

Source: Burchard, R., Huflage, H., Soost, C., Richter, O., Bouillon, B., & Graw, J. A. (2019). Efficiency of platelet-rich plasma therapy in knee osteoarthritis does not depend on level of cartilage damage. *Journal of Orthopaedic Surgery and Research*, *14*(1). doi: 10.1186/s13018-019-1203-0			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Purpose: To study the effects platelet-rich plasma injections have on the levels of cartilage damage in patients with knee osteoarthritis. **Method:** Diagnostic study	Patients were included in this study if they were at least 18 years old, had MRI-diagnosed knee osteoarthritis, ability to walk, and had indications for PRP treatment. Patients were excluded if they were under 18 years old, no signs of osteoarthritis on MRI-imaging, limited knee range of motion less than 90 degrees in flexion and 20 degrees in extension, history of surgery in the last 3 months, fibromyalgia, chronic fatigue syndrome coagulation disorder, thrombocytopenia, recent intra-articular steroid, anesthetic, or viscosupplementation injection in the last 1 year, pregnant patients, and patients with chronic diseases. A total of 59 patients were used in this study.	Once approved by The Medical Ethics Committee of the Medical Council Westphalia-Lippe and informed consent was obtained, subjects were all given a pre-treatment MRI. This was to provide a quantifiable score of the integrity of each patient's cartilage through the WORMS method. PRP was then performed on each patient once per week for three weeks. Visual analog scale (VAS) and WOMAC scores were measured prior to the first injection and following at about 24 weeks following the injections.	Through WORMS scoring, 20.3% patients rated mild, 55.9% rated moderate, and 23.7% rated severe. Results concluded that there was no significant correlation between the degree of cartilage damage in osteoarthritis and a positive response to the patients PRP injections. According to the VAS and WOMAC scores, female subjects showed greater decrease in WOMAC scores than male subjects following the series of PRP injections.
Assessment: When evaluated by the CRAAP test, this article scores 10/10 in currency, 8/10 in relevance, 9/10 in authority, 9/10 in accuracy, and 10/10 in purpose. Overall this article ranks at excellent with 46/50.			

Source: Sîrbu, E., Gligor, Ş., & Pantea, C. (2017). Platelet-rich plasma intra-articular injections as an alternative treatment for knee osteoarthritis: a systematic review. *Timisoara Physical Education and Rehabilitation Journal*, *10*(19), 46–51. doi: 10.1515/tperj-2017-0015			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Purpose: To review the current literature regarding the efficacy of platelet-rich plasma injections as a treatment for knee osteoarthritis. **Method:** Systematic Review	Through the use of PubMed, Embase, and CINAHL databases 319 abstracts were reviewed and a total of 8 relevant articles were identified. These articles included 2 randomized controlled trials with the rest being prospective observation studies and prospective comparative studies.	Utilizing PubMed, Embase, and CINAHL databases, the keywords "platelet-rich plasma", "knee", and "osteoarthritis" were used to cultivate articles. Articles included were studies with human subjects, prospective clinical studies, and full-text articles. Animal studies, retrospective studies, articles not written in English, and articles with patients with previous arthroplasty or ACL surgery were excluded.	The results of this study were inconclusive due to small sample sizes among the included articles. However, it should be noted that the findings of the articles consistently supported the use of PRP in patients with knee osteoarthritis. These articles indicated that PRP may have better effect in patients with early stage osteoarthritis.
Assessment: The design is appropriate at level B when evaluated by the CAT Manager app. Weaknesses of this article include the high likelihood that important studies were not included and the process of extracting data and evaluating data was not reported. Neither the effect size or the CI was included.			

Source: Sucuoğlu, H. (2019). The Short-term Effect of PRP on Chronic Pain in Knee Osteoarthritis. *Ağrı - The Journal of The Turkish Society of Algology*. doi: 10.14744/agri.2019.81489			
Design/Purpose	**Sample/Setting**	**Design Instruments**	**Results**

Purpose: To determine the short-term efficacy in pain relieve of platelet-rich plasma injections in patients with osteoarthritis of the knee. **Method:** Quasi-experimental time series analysis	Subjects included patient of the Physical Therapy and Rehabilitation clinic of the Private Bagcilar Aktif Medicine center who had been dealing with chronic pain for at least 3 months. The patients were enrolled and consented to the study between January 2016 and June 2017 and had grades 2-4 knee osteoarthritis on the Kellgren-Lawrence scale. Subjects were between 40-80 years old.	A total of 3 PRP injections were given to each subject once per week for 3 weeks. Subjects were assessed with the visual analog scale (VAS) at the beginning of the study, at week 3, and then again at week 6. At week 12, they were again assessed with VAS and adverse effects were recorded. The VAS assessed both resting and activity scores.	A total of 37 females and 5 males were included in this study. In the resting and activity VAS scores there was good improvement between the scored observed at the start of the trial and the scores at week 12. The scores were significantly better in K-L grade 2 patients than K-L grade 3-4 patients.
Assessment: The design is moderately appropriate at level B when evaluated by the CAT Manager app. The effect size and confidence interval are not reported, which is a weakness of this article. The trustworthiness of this article is moderate at 70%.			

Appendix B: PEDro Scale Questionnaire

1. Eligibility criteria were specified?
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)?
3. Allocation was concealed?
4. The groups were similar at baseline regarding the most important prognostic indicators?
5. There was blinding of all subjects?
6. There was blinding of all therapists who administered the therapy?
7. There was blinding of all assessors who measured at least one key outcome?
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups?
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by “intention to treat”?
10. The results of between-group statistical comparisons are reported for at least one key outcome?
11. The study provides both point measures and measures of variability for at least one key outcome?

Appendix C: CAT Manager AppQuestionnaire for Systematic Reviews and Meta-analyses

The CAT (Critically Appraised Topic) Manager app, in order to assess systematic reviews and meta-analyses, asks the following questions:

1. Did most included studies use a control group and random assignment?
2. Is it unlikely that important, relevant studies were missed?
3. Was the process to select studies clearly defined and reproducible?
4. Was the process to extract data clearly defined and was the outcome presented in a table?
5. Was the methodology quality of each study assessed?
6. How large was the effect size?
7. How precise was the effect size?

Based upon the answers to these questions, the article is assigned a letter grade which refers to the quality and the level that the article can be trusted.

Appendix D: CAT Manager AppQuestionnaire for Quasi-experimental Time Series Study

The CAT (Critically Appraised Topic) Manager app, in order to assess a quasi-experimental time series study, asks the following questions:

1. Were the criteria used to select subjects clearly defined?
2. Was the intervention (or exposure to a variable) independent of other changes over time?
3. Did fewer than 20% of the subjects drop out?
4. Were reliable and valid measurement methods used?
5. How large was the effect size?
6. How precise was the effect size?

Based upon the answers to these questions, the article is assigned a letter grade, which refers to the quality and the level that the article can be trusted.

Appendix E: CASP Questionnaire

To assess prognostic studies, the CASP (Critical Appraisal Skills Programme) tool was used. The questions used for this appraisal are as follows:

1. Did the study address a clearly focused issue?
2. What the cohort recruited in an acceptable way?
3. Was the exposure accurately measured to minimize bias?
4. Was the outcome accurately measured to minimize bias?
5. Have the authors identified all important confounding factors?
    1. Have they taken account of the confounding factors in the design and/or analysis?
6. Was the follow up of subjects complete enough?
    1. Was the follow up of subjects long enough?
7. What are the results of this study?
8. How precise are the results?
9. Do you believe the results?
10. Can the results be applied to the local population?
11. Do the results of this study fit with other available evidence?
12. What are the implications of this study for practice?

Each question should be answered with a “yes”, “no”, or “unknown”. The more “yes” answers may indicate a more valid study in the context of the question posed (CASP Checklists, 2020).