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Platelets to the Rescue? A Literature Review of the Safety and Efficacy of Platelet-Rich Plasma for Symptomatic Knee Osteoarthritis

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Abstract

Osteoarthritis (OA) of the knee is one of the most common joint disorders in the United States with rising prevalence due to obesity and an aging population. Regarding non-surgical approaches to management, there has been growing interest in the use of intra-articular injections (IAI) of Platelet Rich Plasma (PRP). However, there has been a lack of strong evidence to support its use in clinical practice guidelines.

In this literature review, two search methods were utilized in an effort to, first, inform clinicians about PRP and, second, to shed light on recent clinical control trials regarding the safety and efficacy of IAI of PRP for symptomatic OA of the knee. A comprehensive review of eighteen clinical control trials studies was performed. The primary scope of this review focuses on outcomes related to adverse events and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) for analysis. Other outcomes were also analyzed to evaluate for trends in efficacy. In conclusion, PRP seems to be beneficial for short-term (<6 months) management, especially in younger patients with mild-moderate osteoarthritis. Also, multiple and cyclical injections as well as PRP preparations with concentrated growth factors may be advantageous. The use of $CaCl_2$ in the preparation of PRP appears to have adverse effects. In the mist of overwhelming bias and inconsistencies in study designs and wide variability in PRP preparation, current literature may not provide strong evidence to influence changes to future national guideline recommendations.

Note: This paper does not review non-autologous uses of platelet-rich plasma or platelet-rich plasma co-administered with mesenchymal or multipotent stem cells as those from placenta, adipose tissue, or those derived from any other sources.

Introduction

According to Cisternas et al. (2016), the prevalence of osteoarthritis (OA) in the United States is estimated to have reached 30.8 million (13.4%) between 2008 and 2011. Osteoarthritis of the knee is the most common arthropathy in adults with a global prevalence estimated to be 3.8% in 2010 (Cross et al., 2014). In the United States, osteoarthritis of the knee has an estimated prevalence of 12% in adults greater than 60 years-of-age (Dillon, Rasch, Gu, & Hirsch, 2006). These projections are suspected to further increase due to an obese and aging population (Deshpande et al., 2016).

The pathophysiology of OA has many contributing factors to its development involving the mechanical destruction and repair of articular cartilage. Furthermore, biochemical processes, such as cytokine and anabolic growth factor pathways, contribute to loss of articular cartilage (Ayhan, Kesmezacar, & Akgun, 2014). According to Ayhan et al. (2014), the cycle begins with articular cartilage stress or damage that results in exposure of underlying subchondral bone. This damage stimulates cytokines, such as Interleuikin-1 (IL-1) and Tumor Necrosis Factor (TNF), that are released from damaged cells within the chondral tissue. These cytokines induce nitric oxide synthase and nitric oxide, which contribute to upregulation of proteolytic and collagenolytic enzymes. These proteolytic and collagenolytic enzymes catabolize proteoglycans, collagen fibers, and chondrocytes that give articular cartilage its strength. As the chondral tissue is destroyed, less and less functional articular tissue is available to withstand mechanical stress to the exposed subchondral bone. Overtime, the subchondral bone becomes sclerotic and thickened, osteophytes may form along with a thickened joint capsule. These features contribute to additional pain and limitation in joint mobility (McCance & Huether, 2014, p. 1566). The cyclical nature and progression of the disease makes management difficult and prolonged.

Clinical manifestations of OA stem from symptoms relating to pain and stiffness as well as joint tenderness and deformity. These symptoms tend to progress leading to appreciable loss of joint mobility and function (McCance & Huether, 2014). Osteoarthritis related pain contributes to many aspects of patients' lives including mood, sleep, physical activity, occupation, and overall quality of life. Moreover, the debilitating effects of OA can compromise the physical and psychological health of patients, leading to the development of other comorbid conditions including hypertension, diabetes mellitus, obesity, dyslipidemia, metabolic syndrome, and depression (Leite et al., 2011).

There are many risk factors attributing to the development OA of the knee. Individuals that are older, overweight, or those that have had a history of joint trauma or repetitive joint stress are at higher risk of developing OA(Silverwood et al., 2015). Other risk factors include joint trauma, long-term mechanical stress, joint instability, and congenital or acquired skeletal deformities neurologic disorders. There are also some systemic conditions that may contribute to the rate of cartilage loss. These include, but are not limited to, systemic inflammatory diseases, hematologic or endocrine disorders, and systemic drug interactions (McCance & Huether, 2014, p. 1565).

Today’s treatment for knee OA is directed at improving pain, stiffness, functional capacity, and overall quality of life. Interventions can be divided into pharmacologic, non-pharmacologic, and surgical methods. These interventions are usually guided by symptom severity and personal goals. Initially, lifestyle changes are suggested as preventative measures. Proper diet, weight, and exercise are encouraged in order to maintain lower extremity strength and decrease mechanical stress of the affected joints. As many patients do not seek treatment until symptoms of pain and joint stiffness have already begun, most patients require multiple

treatment modalities to manage symptoms. Conservative approaches include, but are not limited to, the use of analgesics, braces, and mobile assist devices. Oral supplements or disease modifying agents have also been used. More aggressive approaches may be considered with intra-articular injections, especially when other methods have failed to provide symptom relief (Dynamed, 2018). As many of these treatment methods do not address the biochemical progression of the disease, symptoms can become severe enough to require invasive procedures such as arthroscopy or joint replacement surgery.

Osteoarthritis is a prevalent and debilitating disease that can limit activities of daily living and predispose those affected to a higher risk of developing other comorbid conditions. Due to an aging and obese population, OA is a major public health concern with foreseeable financial burden for the global economy (Neogi, 2013). Despande et al. (2016) expresses "the need for the deployment of innovative prevention and treatment strategies for knee OA, especially among younger persons" (Deshpande, 2016, p.3). Regarding non-surgical approaches to the management of knee OA, there has been growing interest in intra-articular Platelet-Rich Plasma (PRP).

Literature Review

Introduction

In this literature review, two different search methods were utilized. The first search method focused on identifying PRP preparation, classification, and barriers that may attribute to current national guideline recommendations. The second search method aimed to evaluate trends in the safety and efficacy in current literature for intra-articular injections (IAI) of PRP in the management of symptomatic osteoarthritis of the knee. The author hopes to contribute to ongoing research aiming to define the optimal PRP preparation, number of injections, and target populations for administration. Moreover, critical review will aim to provide insight more recent studies which may influence future clinical practice guidelines.

Search method

The author searched Cochrane, PubMed, and Dynamed with the following key words applied to titles and abstracts: “platelet-rich plasma”, “autologous-conditioned serum”, “preparation”, “administration”, “physiology”, “theory”, and “therapeutic-use”. There were no inclusion or exclusion criteria. Potential contributing studies were chosen for retrieval and their reference lists were reviewed for retrieval of additional relevant information. All information was formed to provide information relating to the background of PRP.

The author conducted a second search using PubMed database using Mesh terms “osteoarthritis, knee”, “platelet-rich plasma” and the following keywords using “OR” Boolean connector: “intra-articular injections”, “pain”, “stiffness”, “physical function”, “adverse effects”. Articles were further narrowed with application of filters for articles within the past 10 years and human trials. This resulted in twenty-eight articles involving clinically controlled applications of intra-articular PRP for patients with osteoarthritis of the knee. Abstracts of these articles were

further refined and selected based on relevance to clinical questions and excluded if stem cells were used. This resulted in eighteen clinical control trials.

Clinical Application

There is a wide range of clinical applications of PRP with rising popularity in orthopedics and sports medicine. These specialties are interested in PRP because it is thought to aid in healing of damaged tissue. As such, PRP has been used in treating tendinopathy, muscular lesions, muscular fibrosis, spinal fusion, pseudo-arthrosis, arthritis, synovitis, tendinous inflammation, and lesions of the meniscus and articular cartilage (Cerza et al., 2012).

What is PRP?

PRP is synonymous with terms such as autologous conditioned plasma, platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, platelet release formulations, platelet rich in growth factors as well as many others (Willits, Kaniki, & Bryant, 2013). PRP is broadly defined as plasma that has an elevated concentration of platelets, growth factors, and associated proteins above baseline whole blood. Most PRP includes red blood cells (RBC) and white blood cells (WBC) to some extent. (Arnoczky & Shebani-Rad, 2013).

Why are platelets so important?

Platelets contain granules that store numerous growth factors, cytokines, chemokines, and transcriptions factors that are released upon stimulation. These growth factors contribute to the basis of biochemical interactions that are thought to promote healing (Table 1).

Table 1. Growth Factors and Function

Growth Factor	Function
Transforming growth factor-β	Stimulated undifferentiated mesenchymal cell proliferation; regulates collagen synthesis and collagenase secretion; regulates mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophage and lymphocyte proliferation
Basic fibroblast growth factor	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenic for mesenchymal stem cells, chondrocytes, and osteoblasts
Platelet derived growth factor	Mitogenic for mesenchymal stem cells and osteoblasts; stimulates chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis
Epidermal growth factor	Stimulates endothelial chemotaxis/angiogenesis; regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis
Vascular endothelial growth factor	Increases angiogenesis and vessel permeability; stimulates mitogenesis for endothelial cells
Insulin-like growth factor	Bone Maintenance; Cell apoptosis modulation
Connective tissue growth factor	Promotes angiogenesis, cartilage regeneration, fibrosis, and platelet adhesion

Table 2. Note. Modified from both Bashir, J., Panero, A. J., & Sherman, A. L. (2015). The emerging use of platelet-rich plasma in musculoskeletal medicine. *The Journal of the American Osteopathic Association, 115(1),* 27. and Spakova, T., Rosocha, J., Lacko, M., Harvanova, D., Gharaibeh, A. (2012). Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid". *American Journal of Physical Medicine & Rehabilitation, 91(5),* 412.

How does PRP work?

The exact mechanism of action in all applications of PRP has yet to be determined (Arnoczky & Shebani-Rad, 2013). However, the proposed mechanism for cartilage repair is thought to originate from the stimulation of the healing cascade through the influence of high concentrations of growth factors, cytokines, chemokines, and transcription factors released from platelet α-granules (Mascarenhas, Saltzman, Fortier, & Cole, 2015). On a cellular level, these biochemical molecules induce proliferation and differentiation of cells that form extracellular matrix and blood vessels (Alsousou, Thompson, Hulley, Noble, & Willett, 2009). In addition, cellular chemotaxis promotes recruitment of macrophages that remove tissue debris (Bashir, Panero, & Sherman, 2015). Furthermore, growth factors are thought to contribute to the proliferation of mesenchymal stem cells and chondrocytes as well as the inhibition of catabolic cytokines such as interleukin-1β, tumor necrosis factor-α, and interlukin-6 (Mascarenhas et al., 2015). These cellular interactions optimize metabolic activity and nutrient delivery to damaged tissue to ultimately influence the repair and healing of chondral tissue.

Preparation and Administration

There are many proposed methods of PRP preparation. Most methods and techniques for PRP preparation are standardized into specific kits with instructions. These may include, but are not limited to, the use of gravitational platelet sequestration techniques, standard cell separators, and plateletpheresis (Alsousou et al., 2009). Administration can be through liquid, gel, spray or clot media depending the situation (open or closed articular surface) and physician preference (DeLong et al, 2012). Of note, this review will only focus on intra-articular, closed articular surface, PRP application.

The process begins with a collection of the patients own blood, usually in combination with citrate dextrose-A or citrate phosphate dextrose. The addition of anticoagulants is thought to inhibit the clotting cascade within the serum, preserve the metabolic needs of platelets, and aid in platelet separation from other cellular components (Arnoczky & Shebani-Rad, 2013). Contrarily, some methods do not require anticoagulant, especially if the PRP is administered before clotting has been initiated (Willits et al., 2013).

After the blood draw, the sample is centrifuged one or multiple times to isolate and concentrate cellular components (DeLong, Russel, & Mazzocca, 2012). The first centrifuge separates RBCs and WBCs. After separation, a portion of the serum is removed using a filter or separation system. Subsequent centrifuges are utilized to further concentrate cellular components and/or reduce remaining RBCs and WBCs within the serum (Willits et al., 2013).

In general, preparations can be classified into two categories; plasma-based preparations and buffy-coat preparations. Plasma-based methods aim to isolate only plasma and platelet components within the final product. This method favors the exclusion of leukocytes or other cellular contents and is achieved through slower and shorter centrifuge cycles and multiple filtrations. Of note, multiple filtrations may contribute to greater platelet loss. Buffy coat-based methods aim to obtain the highest platelet concentration, however this may allow greater amount of other cellular components in the final product. Typically, buffy coat-based methods use faster and longer centrifuge cycles with less filtration (DeLong et al., 2012). Most methods of preparation try to limit WBC in the final product because they are thought to release proinflammatory substances which can be detrimental to the healing process (Cerza et al., 2012).

Prior to injection, some methods “activate” the platelets, or promote the clotting cascade, with the addition calcium chloride and/or thrombin. It is proposed that “activation” of platelets

promotes formation of a fibrin scaffold which stimulates the release of growth factors. This intensified release of growth factors is thought to ultimately contribute to higher concentrations of bioactive molecules, thus sustaining PRPs beneficial effects for longer duration (Arnoczky & Shebani-Rad, 2013). In the same manner, some commercially available systems use other endogenous or exogenous methods to activate platelets (DeLong et al., 2012). It is proposed that platelet activation also takes place when platelets are introduced into the synovial joint where natural activation factors are present. Within the literature there has also been growing interest in the addition of isolated cytokines or mesenchymal stem cells into the PRP final product (Baltzer, Moser, Jansen, & Krauspe, 2009. "see also" Koy & Choi, 2012).

PRP Classification

As described above, there is a wide variety of preparation methods, each promoting a unique variation of PRP product. In response, there have been many proposed classification systems aiming to define the quantity and quality of final product. Currently, there is no widely accepted classification system for PRP. This is primarily due to the lack of evidence-based studies that define the optimal concentrations of cellular components (Arnoczky & Shebani-Rad, 2013). Aside from these barriers, most platelet derived products can be classified into four general categories. These categories are based on method of preparation and platelet activation and include: leukocyte-poor PRP (LP-PRP), leukocyte-rich PRP (LR-PRP), pure platelet-rich fibrin clot, and leukocyte platelet-rich fibrin clot. There have been many other classifications systems that have been proposed to further classify PRP. An example of such a system is the Platelet Activation White blood cells (PAW) classification system. This system is based on the absolute number of platelets, type of platelet activation, and presence or absence of white cells (DeLong et al., 2012).

PRP and National Guideline Recommendations

There are several issues to consider when critically evaluating PRP within the literature. There are many variables to consider including: volume of blood that is drawn, concentration of platelets, presence of other cellular components in the final product, means of platelet activation, number of injections required, and length of time between injections. Undoubtedly, these many variables prove to be a big hurtle in developing research methods and clinical study. And, consensus amidst, the research does not yet lend overwhelming support towards IAI of PRP treatments for symptomatic OA of the knee in current national guidelines. In reflection of current clinical guideline recommendations, the American Academy of Orthopedic Surgeons (2013) does not recommend nor disapprove the use of IAI of PRP for the treatment of symptomatic OA of the knee (Table 2).

Table 2. American Academy of Orthopedic Surgeons: Treatment of Knee Osteoarthritis

RECOMMENDATION 10

> "We are unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee"
>
> Strength of Recommendation: Inconclusive

American Academy of Orthopedic Surgeons (AAOS) grading system for strength of recommendations
Strong - benefits clearly exceed potential harm and/or quality of supporting evidence is high (based on ≥ 2 high-strength studies with consistent findings)
Moderate - benefits exceed potential harm but quality/applicability of supportive evidence not as strong (based on ≥ 2 moderate-strength studies with consistent results or evidence from 1 high-strength study)
Limited - quality of supporting evidence is unconvincing, or well-conducted studies show little clear advantage to one approach over another. (based on ≥ 2 low-strength studies with consistent results or evidence from 1 moderate-strength study)
Inconclusive - lack of compelling evidence with unclear balance between benefits and potential harm (based on 1 low-strength study or otherwise conflicting evidence)
Consensus - expert opinion supports recommendation despite no available empirical evidence meeting inclusion criteria of guideline's systematic review

Table 1. Note. Adapted from "Treatment of Osteoarthritis of the Knee" (2013). American Academy of Orthopedic Surgeons, 2nd ed. The American Academy of Orthopedic Surgeons. PP. 854

Research Questions

In patients with symptomatic osteoarthritis of the knee, is platelet rich plasma safe?

In patients with symptomatic osteoarthritis of the knee, does platelet rich plasma improve pain, stiffness, and physical function?

In patients with symptomatic osteoarthritis of the knee treated with platelet rich plasma, does one injection versus more than one injection improve pain, stiffness, and physical function?

In patients with symptomatic osteoarthritis of the knee treated with platelet rich plasma, are there a trend in the type of PRP that is most effective terms of pain, stiffness, and physical function?

In patients with symptomatic osteoarthritis of the knee treated with platelet rich plasma, does severity of OA effect treatment outcomes in terms of pain, stiffness, and physical function?

In patients with symptomatic osteoarthritis of the knee treated with platelet rich plasma, does age effect treatment outcomes in terms of pain, stiffness, and physical function?

In patients with symptomatic osteoarthritis of the knee treated with platelet rich plasma, does BMI effect treatment outcomes in terms of pain, stiffness, and physical function?

Critical Review of Control Trials

A study conducted by Garcia-Escudero and Hernandez Trillos (2015) evaluated the use of autologous conditioned serum (ACS) in conjunction with physiotherapy in patients with unilateral symptomatic knee osteoarthritis. A total of 118 patients received one IAI of ACS for four consecutive weeks in combination with physiotherapy for fifty minutes per week. Outcomes were evaluated using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Numeric Rating Scale (NRS) at 0 and 24-months and 0, 3, 6, 12, and 24-months respectively.

This study design did not have comparative group allocation or establishment of a control group. However, the study design allowed for comparative study analysis. The population demographics and characteristics were disclosed with no statistically significant difference between groups. It was noted that patients enrolled in the study were considering knee surgery,

which may attribute to sample bias favoring more symptomatic patient population. Moreover, most patients in this study were classified with Kellgren-Lawrence (KL) Grade 3 knee OA. Patient follow-up was >90% with only one patient lost to follow up. Statistical analysis was discussed at length with effect size of most WOMAC scores ranging from 8 to 13.6 except WOMAC subscale for stiffness. Of note, PRP that was to be administered for subsequent injections was frozen.

All injections were tolerated well with no severe adverse effects. Regarding efficacy, there was a statistically significant improvement in NRS for pain compared to baseline at 3, 6, 12, 2-months ($p < 0.001$ for each). Also, global WOMAC and WOMAC subscales for function and pain had statistically significant improvement from baseline at 24-months ($p < 0.001$ for each). However, there was no significant improvement in the WOMAC subscale stiffness ($p > 0.6$). Regarding OA severity, there was statistically significant improvement of global WOMAC from baseline in all grades of severity (KL Grade 1-4) ($p > 0.001$ for each group). This study found that there was not enough data to make a reliable analysis or correlation between clinical improvement and demographics for age, gender, BMI, or severity of OA. There was limited data to contribute to this review's outcome measurements because WOMAC scores were only measured at 0 and 24-months.

Filardo et al. (2012a) compared the safety and efficacy of single-spin vs double spin approach to PRP preparation. In this study, 114 patients were allocated into two groups, each received either three IAIs of plasmat-rich growth factor (PRGF) (single spin) or three IAIs of PRP (double spin) at 3-week intervals. Outcomes were measured using the International Knee Documentation Committee (IKDC) score, Visual Analogue Scale (VAS), and Tenger activity

scale. Also, adverse effects were evaluated on a clinical basis and satisfaction was evaluated at final follow-up. All patients were evaluated at base-line, 2, 6, and 12-month follow-up.

This study had a no statistically significant difference in demographics or baseline outcome scores. Results were displayed in charts and tables with disclosure of software used for statistical analysis. All patients were accounted for in the statistical data. Unfortunately, this study has many weaknesses. The methodology of this study did not randomize patient selection or group assignment. Also, there was no blinding or control. There was inconsistency between the PGRF and PRP product storage. The PRGF product was drawn at each visit and administered immediately after preparation. In comparison, the PRP product drawn at one visit and was refrigerated for subsequent injections. When analyzing the preparation method, there was significantly more blood drawn from patients receiving PRP. As intended, the PRP group had significantly higher platelet concentration in the product, however, this is misleading in differentiation between the two methods of preparation. It was difficult to assess validity of the charts and tables that were used in this article due to lack of raw data. Moreover, calculating effect size was not possible due to lack of raw data.

This study was unique in that it focused on finding the difference between platelet preparation methods and final product in terms of platelet concentration, cellularity, and storage that may contribute to its clinical effect. Of note, regarding cellularity evaluation, platelet concentrations of PRP and PRGF was 949,000/ul and 315,000/ul respectively. Also, there was a mean absolute WBC count of 8,300/ul in the PRP group and none in the PRGF group. Overall, there were no severe adverse events. However, there was a statistical significance in pain and swelling after injection in those that received PRP (double spin) compared to PRGR (single spin) ($p = 0.03$ and $p = 0.0005$ respectively).

Regarding efficacy, the PRGF group and PRP group showed statistically significant improvement in IKDC subjective score from baseline at 2, 6, and 12-month follow-up ($p <$ 0.0005 for each in both cases). Contributing to these outcomes, EQ-VAS and Tegner scores also showed statistically significant improvement in both the PRGF group and PRP from baseline compared to 2, 6, and 12-month follow-up ($p < 0.0005$ for each in both cases). There was no statistical difference between groups regarding IKDC, EQ-VAS, or Tegner scores at 2, 6, and 12-month follow-up ($p > 0.05$). Also, end-of-study satisfaction had similar results in both groups. Regarding age, this study observed less improvement in IKDC scores in older patients at 12-month follow up for both PRGF and PRP group ($p = 0.009$ and $p = 0.012$ respectively). Regarding OA severity, there was statistically significant improvement in IKDC subjective scores from baseline for all those with cartilage degeneration (KL Grade 0), early OA (KL Grade 1-3), and advanced OA (KL Grade IV) ($p < 0.05$ in each case in each group). Moreover, there was no statistically significant difference in IKDC score between PRGF and PRP at 2, 6, or 12-month follow-up ($p > 0.2$ for each follow-up). However, in both the PRGF and PRP groups there was a trend of more improvement of IKDC scores in those with less severe cartilage degeneration.

Gobbi, Lad, & Karnatziko (2015) evaluated the effectiveness of cyclical doses of PRP in relieving symptoms in the early stages of OA. In this study, 93 patients (119 knees) were allocated into two groups. Both groups received one cycle (three intra-articular injections at one-month intervals), and Group 2 received an additional second cycle at one year. Outcomes were assessed using the Knee-injury and Osteoarthritis Outcome Score (KOOS), VAS, Tegner, and Marx scales. Follow-ups were scheduled at 12, 18, and 24 months.

The population demographic characteristics in this study show no statistical differences between groups. Randomized allocation was performed using computer software. All patients were accounted for throughout the study. Subjects form this study were all involved in recreational sports, which was another variable when compared to other studies of its kind. Although this study seems to be well designed, there were many notable weaknesses. This study lacked blinding of subjects or clinicians and there was no establishment of a control group. Also, there was an issue regarding adherence to administration of the second cycle of injections in Group 2. These patients had shifted from Group 2 to Group 1 because they did not feel it was necessary to receive a second cycle of injections. This reassignment may attribute to bias when analyzing the statistical data. In attempt to avoid bias, the author used modified intention to treat analysis. Patients were also allowed to have either one or both knees involved in the study. Another variable that may contribute to bias is that the study design allowed bilateral knee enrollment. As individual scores were recorded for each knee individually, the subjective score of one knee could affect the scores recorded for the contralateral knee. Furthermore, the power of this study was not discussed, and effect size could not be calculated.

In conclusion of this study, both groups had significant improvement of KOOS, VAS, Tegner and Marx scores at 12, 18, and 24-month follow-up compared to baseline ($p < 0.001$ for each in both cases). When comparing the two groups, there was a statistically significant difference in VAS and Marx scores with a greater improvement at 18-months in patients who had received the second cycle of injections ($p < 0.001$).

Jang, Kim, & Cha (2013) analyzed the difference between the degree of knee joint degeneration and efficacy of a single IAI of PRP. Patients were placed in to three categories

based on KL grade (KL grades I, II, and III). Outcomes were assessed using the IKDC and VAS score with evaluation at 1, 3, 6, 9, and 12-months.

This study did not discuss the method of preparation of PRP nor the concentration of platelets that was administered. This study design did not have a control group nor randomize patient selection. The patient population was primarily female and there was no discussion of patient follow-up or patient accountability. Although charts and tables were utilized, there was no raw data values available to validate the represented data. It is of importance to note that twenty-five patients in this study had bilateral knee treatment with PRP which may attribute to bias. The only relevant results from this study was that the PRP treatment showed longer lasting effects in subjects with KL grade I compared to KL grade III in regard to VAS score ($p < 0.05$)

Patel, Dhillon, Aggarwal, Marwaha, and Jain (2013) compared the use of a single or double injection of PRP versus placebo. A total of 78 patients (156 knees) were randomly allocated into three groups. Group A received a single IAI of PRP, Group B received two IAI of PRP at 3-week intervals, Group C received single IAI of normal saline. Outcomes were measured using WOMAC, VAS, overall satisfaction, and adverse effects at 3-weeks, 3-months, and 6-month follow-up.

This study design had a control group unlike other studies under review. Also, there was randomization for patient selection and allocation into assigned groups. It was noted that double-blinding was incorporated through trained medical assistants. Population demographics and characteristics of each group were discussed at length with no statistically significant difference between groups. All subjects in each group were treated equally through the study, and all patients were accounted for in this study with patient follow-up greater than 90%. The use of

tables and charts represented the results well. Disappointingly, the power of this study was not discussed, and the effect size could not be calculated due to lack of raw data.

When assessing adverse effects, both PRP groups had a syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia with higher incidence in the group that received two IAI of PRP. Regarding efficacy, there was a statistically significant difference in WOMAC in Group A compared to Group C in favor of Group A at all follow-up visits ($p < 0.001$ for each). Similarly, there was a statistically significant difference in WOMAC in Group B compared to Group C in favor of group B at all follow-up visits ($p < 0.001$ for each). There was a statistically significant reduction in pain as assessed by VAS scores compared to baseline for group A and group B ($p = 0.001$ in each case) but not in Group C (P=0.598). Interestingly, there was no statistically significant difference in VAS scores when comparing Group A to Group B at any follow-up period ($p > 0.05$). Satisfaction was rated satisfied, partially satisfied or not satisfied by the patient. Results found that 67.3%, 64%, 4.3% were satisfied in group A, B, and C respectively. There were no trends observed in efficacy regarding patient demographics including age, sex, or BMI in group A or B. However, in both group A and B, there was a trend in WOMAC scores that showed continued improvement up to 3-month follow-up with slight decline by 6-month follow-up.

Rayegani et al. (2013) conducted a study that evaluated the effects of PRP in combination with exercise and stretching. In this study, 65 patients with unilateral knee OA were randomly allocated into two groups. Group 1 received two injections of PRP at 4-week intervals. Group 2 did not receive any intra-articular injections. Both groups were educated and instructed to perform isometric exercise of muscles around the knee as well as stretching of the hamstrings three times a day. Outcomes were assessed using WOMAC at 4-weeks, 8-weeks, and 6-months.

This study had many weaknesses. The study design was not blinded and did not have a formal control group. Population demographics were balanced between groups; however, the majority of subjects were female. The study design permitted administration of acetaminophen prior to PRP injections which may contribute to subjective bias. However, the author's statistical analysis showed no correlation between amount of acetaminophen consumption and the amount of response to treatment. Also, there was wide variability in platelet concentration and WBC count in both whole blood and final PRP product. Patient follow up was >90% in both groups with only three patients lost to follow-up. Effect size was not discussed and could not be calculated due to the lack of control group and available raw data.

First, there was no significant relationship between the platelet concentration and response to treatment ($p > 0.05$). Second, there was statistically significant improvement of symptoms both exercises only and PRP with exercise groups compared to baseline for pain ($p = 0.007$, $p = 0.001$ respectively), stiffness ($p = 0.014$, $p = 0.001$respectively), and functional capacity ($p = 0.001$, $p = 0.001$ respectively). Third, there was no statistically significant difference in WOMAC sub-groups for stiffness or functional capacity between the two groups ($p = 0.17$, $p = 0.09$ respectively). However, there was a statistically significant difference in WOMAC subscale for pain ($p < 0.05$) in favor of PRP.

Sampson, Reed, Silvers, Meng, and Mandelbaum (2013) conducted a pilot study of fourteen patients to evaluate PRP injection effectiveness in the treatment of OA symptoms. No groups were assigned, and all subjects received three IAI of PRP at 4-week intervals. Outcomes were assessed using VAS and KOOS with follow-up at 2, 5, 11, 18, 52-weeks. Also, cartilage thickness was measured using ultrasound at baseline and 6-months. Satisfaction was also assessed at 12-month follow-up.

This study had very small sample size and lacked a control group for comparison analysis. Population demographics and characteristics were not discussed. Of note, twelve out of fourteen patients were male. There also was a discrepancy between the amount of blood that was drawn and the PRP that was obtained. As the volume of blood that was taken was substantially higher than what was needed to obtain 6 mL PRP. It was presumed that 54 mL of blood was drawn and divided into three different vials and two were stored for subsequent injections. All patients were accounted for and only one patient was lost for undisclosed reasons. Statistical methods of this study were discussed at length, however there was limited raw data to validate findings. Moreover, the power of this study was not disclosed, and calculation of effect size was not possible.

Smith (2016) conducted a study that focused on the safety and effectiveness of LP-PRP. Two groups were allocated to receive three IAI of LP-PRP or saline at 1-week intervals. Injections were administered on a weekly basis and patients returned for follow evaluation at 1-week, 2-weeks, 2-months, 3-months, 6-months, and-12 months. Outcomes were assessed with WOMAC score as well as adverse effects.

This study was randomized, double-blinded, and placebo controlled. Both subject and clinician blinding was performed through trained medical assistants whom completed blood draws, prepared injections, and covered syringes. Statistical analysis and methods were discussed at length. Population characteristics were statistically similar in both groups and all patients were treated similarly through the study. Of note, the population was limited to only using patients that had already established care with the author. There was no discussion about patients lost to follow-up. However, analysis of end-of-study results indicate that there was 100% follow-up. The power of this study was calculated to be 1.0 as with an effect size of 2.78.

In this study, subjects that received PRP had a statistically significant reduction in WOMAC scores compared with baseline and placebo ($p = 0.005$ and $p \leq 0.001$ respectively). These beneficial effects were sustained through the duration of the study with no negative adverse effects.

Baltzer, Moser, Jansen, and Krauspe (2009) compared the effects of ACS with interleukin-1 receptor agonist (IL-1Ra) to Hyaluronic acid (HA) and placebo. The study involved 376 patients that were randomly assigned into three groups. Group 1 received six IAIs of PRP two times a week for three consecutive weeks. Group 2 received one IAI of 1% solution HA weekly for three consecutive weeks. Group 3 received two IAI of normal saline weekly for three consecutive weeks. Patients were evaluated at 7,13, and 26-weeks after last injection. Eligible patients were followed prospectively for two years. Outcomes assessed with VAS, WOMAC, Short-Form 8 Health-Related Quality of Life (SF-8 HRQL) survey, and patient satisfaction using Global Patient Assessment (GPA) as well as adverse events.

This study had many strengths. Baseline demographics were not statistically different, except for age. The age differences in mean age was lower for the ACS group compared to HA and placebo group. All patients were treated similarly throughout the study. All patients were accounted for throughout the study with >80% follow-up at final assessment. Statistical method of analysis was discussed at length, and results were well represented in graphs and tables. Intent-to-treat analysis was performed for outcome of primary and secondary variables as well as safety analysis. Power was discussed and found to be >80%.

There were some weak points within this study. Inclusion criteria selected patients that had KL grade 2-3, VAS of at least 50/100, which may contribute to sample bias toward more aggressive manifestations of OA. Patients were able to include both knees to receive injections

and the more painful of the two knees was treated initially while the other knee was treated three to six months later. Although this may contribute to bias the second knee was not included in the study analysis. However, initiation and analysis of the more severe knee may also contribute to bias toward more severe manifestations of OA. One major point that is subtle within the article was the ACS group received a total of six IAIs compared to three IAIs in the HA and saline groups which may contribute to bias. Also, the study design was not uniformly blinded. Double-blinding was only performed for the first 6-months. At the second-year follow-up only the patient was blinded which may contribute to bias. Effect size and other independent statistical analysis was not possible due to limitations in disclosure of raw data.

Regarding safety, the ACS group had mild and moderate adverse reactions immediately after injection. All observed adverse effects were local and included symptoms such as pressure, transient pain, swelling, tenderness, and heat at the injection site with improvement within minutes up to one day. There was no statistically significant difference in adverse events observed between ACS and saline group ($p > 0.05$). Regarding efficacy, the ACS group statistically significant improvement compared to placebo in all WOMAC subscales at all follow-up visits ($p < 0.001$ for each at each follow-up period). Also, there was statistically significant difference in VAS scores at 7, 13, and 26 between ACS in comparison to placebo with lower scores in those that received ACS ($p < 0.001$ for each).

Duymus et al. (2017) compared the efficacy of PRP to HA and ozone gas in patients with mild to moderate knee OA. A total of 102 patients were selected and randomly assigned to three groups. Each group received either two IAI of PRP, one IAI of HA, or four intra-articular infiltration of ozone. Outcomes were assessed using WOMAC and VAS at 1, 3, 6, and 12-months.

All patients were accounted for through the duration of this study and follow-up was >80% at the end of the study. Statistical analysis was discussed at length with disclosure of software that was used. Unfortunately, this study had many weaknesses. Most of the sample population was female, although there was equal distribution with no statistical difference between treatment arms. There was no mention of how platelets were stored for subsequent injections. Overall, the power of this study was discussed to be at least 80%.

Cerza et al., (2012) conducted a study comparing the efficacy of platelet-rich plasma and hyaluronic acid (HA) in patients with knee osteoarthritis. The study involved 120 patients that were randomized into two groups. Groups received four IAI of either PRP or HA at weekly intervals. Outcomes were evaluated using WOMAC score at baseline and at 4,12, and 24-weeks.

In critical analysis of this study there was found limited bias. There was no statistically significant difference in patient demographics for age, gender, OA severity, or baseline WOMAC scores ($p > 0.05$ in each case). No patients were lost throughout the duration of the study with a follow-up of 100%. Throughout the study, patients were treated similarly with consistent blinding. Of note, the physician that administered injections was unblinded. Statistical analysis was discussed at length. Power of the study was >80% with an effect size > 0.8.

Overall, there was number of findings in this study. No adverse reactions were observed in either group at any follow-up time period. The PRP group, observed a statistically significant difference in WOMAC total from baseline at 4, 12, and 24-weeks ($p < 0.001$ for each). Also, there was statistically significand difference in WOMAC total from baseline at 4 and 12-week follow-up and between 4 and 24-week follow-up ($p < 0.001$ in each case). Of note, there was no difference in WOMAC total between 12 and 24-week follow-up ($p = 0.007$). Regarding the efficacy of PRP and OA severity the PRP group had no statistically significant difference

between OA severity (KL grade 1-3) and WOMAC total at 4, 12, or 24-weeks ($p < 0.05$ for each). Regarding outcome measures, there was a lack of available raw data from the WOMAC scores. It was presumed that only the total WOMAC score was available and there was a lack of mean WOMAC scores for subscales for pain, stiffness, and physical function. This limited contribution in comparison to other studies in evaluation of efficacy.

Cole, Karas, Hussey, Pilz, & Fortier (2017) compared the clinical and biological effects of PRP versus HA in patients with mild to moderate knee OA. In this study, 111 patients were randomly allocated into two groups. Both groups received three IAI of either PRP or HA weekly for three consecutive weeks. Outcomes were assessed using WOMAC pain sub-scale, IKDC, VAS for pain, and Lysholm knee score at 2, 3, 6, 12, 24, and 52- weeks. Biochemical marker concentrations were also measured through synovial fluid analysis at baseline, 12, and 24-weeks post injection.

The study design was consistent in blinding methods and group randomization was performed using computer software. Statistical methods and analysis were discussed at length. All patients were accounted for in this study with patient follow-up was >80%. Population demographics were balanced except for a statistically significant difference in Body Mass Index (BMI) with lower BMI in the PRP group ($p = 0.05$).

In this study, there were a many relevant observation of interest. In the PRP group, there was statistically significant improvement from baseline in IKDC score at 2, 3, 6, 12, 34, and 52-weeks ($p < 0.05$ for each). Also, in the PRP group, there was a statistically significant improvement from baseline VAS score from baseline at 12 and 24-weeks ($p < 0.05$ for each) but not for 52-week follow-up ($p > 0.05$). Regarding subject demographics, patients with KL Grade 1 had statistically significant improvement in IKDC score compared with those with KL Grade 3

changes ($p < 0.05$). Also, there was a statistically significant improvement of IKDC scores seen in those with lower BMI (BMI 18.5-24.9) compared to those with that were obese (BMI >30) ($p < 0.05$). Interestingly, synovial joint fluid analysis in the PRP group found that there was a trend toward lower levels of interleukin-1β and tumor necrosis factor α compared to baseline ($p = 0.06$ and $p = 0.68$ respectively).

Lisi et al. (2017) compared the efficacy of PRP versus HA in patients with OA of the knee. In this study, 58 patients were randomly assigned to one of two groups. Group 1 received three IAI of PRP at 4-week intervals. Group 2 received three IAI HA at 4-week intervals. Outcomes were assessed using WOMAC, Lysholm, Tegner, American Knee Society Score (AKSS), Lequesne, and VAS at baseline, 15-days, 6-months, and 12-months. Patients were also subject to Magnetic Resonance Imaging (MRI) with evaluation of improvement of cartilage degeneration at baseline and 6-months.

This study was unique in that MRI evaluation was used to compare differences in chondral degeneration at the end of the study. It was disappointing to find that the classification system used to grade OA severity was not consistent with other studies that used imaging. Also, it was not clarified weather the same technician was used to evaluate OA grade. This study was randomized but lacked a placebo group. There were limitations in patient and clinician blinding throughout the study that may contribute to bias. Analysis of patient demographics found that there were no statistically significant differences in baseline outcome scores or population demographics between the two groups. Although patient follow-up was discussed, not all patients were accounted for, there was limited discussion for reasonings for losses. Also, bilateral knee enrollment was allowed which may contribute to bias. Overall, this study had a small sample size which diminishes the strength of this study.

The only relevant information attributable to this review was the observation of no side-effects with IAI of PRP. All other outcome measurements were too high risk for bias or did not provide enough data to contribute to analysis of efficacy.

Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh (2012) evaluated the safety and efficacy of PRP injections for OA of the knee and tried to identify factors that may influence accessibility and cost of PRP preparation in the clinic setting. The study included 120 patients that were randomly assigned to receive three IAI of PRP or HA at weekly intervals. Outcomes were assessed using WOMAC and Numeric Rating Scale (NRS) at baseline, 3, and 6-months.

The study design had no control group or blinding. There was no statistically significant difference in patient demographics or baseline outcome scores between groups. Of note, most patients were classified as having KL Grade 2. The methods of statistical analysis were disclosed with the use of graphs, however most data was conveyed through text.

Results of the study found that there was no major adverse events or complications with IAI PRP. However, there was mild worsening of pain in six cases which resolved within two days. Regarding efficacy, statistical analysis for WOMAC subscales could not be utilized due to the lack of raw data.

Kon et al. (2011) conducted a study that evaluated the efficacy of PRP versus low molecular weight (LMW) and high molecular weight (HMW) HA. This study involved 150 patients that were randomly allocated into three groups to receive either PRP, LMW HA, or HMW HA. Patients were evaluated using IKDC, EQ-VAS at baseline, 2, and 6-month follow-up. Adverse events were also recorded throughout the study as well as overall satisfaction at final follow-up.

Like other comparative studies, there was no establishment of a traditional control group or methods of blinding. Randomization was performed; however, methods of randomization were not disclosed. Patient demographics were statistically balanced, except for statistically significant difference in BMI with the group receiving LMW HA having lower BMI compared to the other two groups ($p = 0.004$). Of note, patient follow up was not disclosed, and the number of patients lost to follow-up could not be analyzed. Statistical analysis was discussed at length with good representation of data using charts and tables.

Throughout this study, there were no complications were observed at any follow-up period. Regarding efficacy, PRP showed statistically significant improvement of IKDC score from baseline at 2 and 6-months ($p < 0.05$ for each). Also, regarding age, there was a statistically significant difference in IKDC at 6-month follow-up in subjects that were less than 50 years compared to those that were older than 50 years in favor of those that were less than 50 years ($p = 0.004$). Regarding OA severity, there was more improvement in IKDC score from baseline and 6-month follow-up in patients effected by those with evidence of chondral degeneration (KL Grade 0) compared to early OA (KL Grade 1-3) and advanced OA (KL Grade IV) ($p = 0.004$ and $p < 0.005$ respectively). Also, PRP group had a satisfaction rate of 82% at the end of the study.

Gormeli et al. (2017) compared the clinical effects of multiple doses of PRP and HA in different stages of OA. This study consisted of 162 patients that were randomly divided into four groups. Group 1 received three IAI of PRP. Group 2 received one IAI of PRP followed by two IAI saline. Group 3 received three IAI of HA. Group 4 received one IAI of normal saline. The four groups were further dived into two sub-groups differentiated by grade of OA severity (KL grade). Sub-groups were defined as either having early OA degeneration (KL grade 0-3) or severe cartilage degeneration (KL grade IV). Patients were assessed using EuroQol Visual

Analogue Scale (EQ-VAS), IKDC, and satisfaction at baseline and 6-month follow-up. Adverse events were also recorded.

This study had many strengths. There was no statistically significant difference baseline characteristics between groups. The proportion of sub-groups were similar in number. All patients were treated similarly in each group and patient follow up was >80%. Double-blinding was performed using "study assistants" that kept treatment and patient information concealed. There were very few weaknesses in this study. The most significant weakness of this study was that the study duration was short with prolonged follow-up visits compared to other studies under review. Also, PRP that was to be administered at subsequent visits was refrigerated. The storage of platelets in freezing conditions may change the morphology and decrease platelet functional properties which may interfere with the degranulation of alpha-granules (Filardo et al, 2012b). Overall, the proposed power of this study was >80% with an effect size greater than or equal to 0.8.

At 6-month follow-up, all groups showed improvement compared to control group ($p < 0.05$) and patients that had received three PRP injections had significantly better results compared to those that received one PRP injection ($p = 0.001$). Interestingly, when analyzing sub-groups, there was a correlation between the response to treatment and severity of OA. In patients with early OA, there was significant difference from baseline in all three groups compared to control group ($p < 0.005$). Also, there was a significant improvement in those that received three injections of PRP compared to a single injection of PRP ($p = 0.001$). In patients with more advanced OA, there was significantly better results in all treatment groups compared to control ($p < 0.05$). However, in patients with severe OA, there was no significant difference in

post-treatment response between those that received three injections of PRP versus merely one injection of PRP ($p < 0.05$).

A study conducted by Filardo et al. (2015) evaluated the benefits of PRP compared to HA in patients with early stages of knee joint degeneration. The study enrolled 192 patients that were randomly allocated into two groups. Each group received three IAI of either PRP or HMW HA at 1-week intervals. Outcomes were measured using IKDC, KOOS, EQ-VAS, Tegner, range of motion, trans-patellar circumference at base line 2, 6, and 12- months. End study satisfaction was also recorded as well as adverse events throughout the duration of the study.

Study design did not have a formal control group. Patients that were enrolled in this study were not randomly selected, rather, voluntary enrolment was utilized through advertisements in journals and websites. Population demographics between the two groups had no statistically significant difference except for age. The PRP group had a lower mean age ($p = 0.024$) compared to the other allocated group. Methods of blinding and randomization were discussed at length and each group was treated similarly through the duration of the study. All subjects were accounted for with >90% follow-up in each group. Sample size and statistical result analysis were also discussed at length. PRP preparation that was to be administered at subsequent visits was refrigerated.

There was statistically significant improvement in IKCD and Tegner activity score in the PRP group from baseline at 2-months ($p < 0.005$ and $p < 0.0005$ respectively). These effects were sustained up to 12-months in these outcome parameters. Also, in the PRP group, there was a statistically significant difference in EQ-VASD from baseline compared 12-month follow-up ($p = 0.006$). There were no significant changes in ROM at any point in the study in the PRP

group. Also, of note, there were no major adverse effects associated with IAI of PRP. However, PRP group had frequent transient self-limited swelling and pain after injection.

Filardo et al. (2012b) compared the efficacy of IAI of PRP to IAI of HA in the treatment of knee OA. In this study, 109 patients were randomly divided into two groups. Each group received three IAI of PRP or HA at one-week intervals. Outcomes were measured using IKDC, EQ-VAS, Tegner, KOOS, range of motion, knee circumference, satisfaction, and adverse events. Outcomes were recorded at baseline, 2, 6, and 12-months.

In this study, patients were assigned to groups randomly and double-blinding was performed by independent medical staff. The population sample was found to have no statistically significant difference in demographic characteristics. Statistical analysis was discussed at length. There were some weaknesses to this study that contribute to bias. Like other studies that involved cycles of PRP injections, the final product of PRP was refrigerated for subsequent injections. Also, the method of anticoagulation and platelet activation was not disclosed. Overall, the strength of this study was questionable. It was noted that the power of this study could not be determined because the sample population did not meet the minimum sample size requirements. Also, the size of effect could not be calculated due to the lack of control and available raw data.

Results of this study found that there were no major complications were observed during the follow-period. However, there were a few self-limiting reactions that lasted a few days. Interestingly, PRP group had significantly higher post injective pain reactions when compared to HA ($p = 0.039$). Regarding severity of OA and treatment efficacy, this study did not find a statistically significant difference in efficacy between PRP and HA in patients with severe OA (KL Grade III). However, a trend was observed that approached statistical significance regarding

patients with less severe OA (KL Grade <III) with efficacy favoring PRP compared to HA at 6- and 12-month follow-up ($p = 0.08$ and $p = 0.07$ respectively). Most importantly, both groups had improvement compared to baseline.

Discussion

Safety

The benefits of receiving any type of intra-articular injections must be weighed against the potential risks. It is proposed that, compared to other types of IAI, the derivation of autologous blood as used in PRP products may advert anaphylactic reactions or disease transmission. However, due to the diverse nature of PRP preparation and wide variety in final product, the safety of PRP has been a major controversy. With variations in PRP final product, mainly regarding platelet and leukocyte concentration and addition of anticoagulants and activation factors, there was need to analyze if any of these variations contributed to adverse effects. Appendix A, Table 3, summarizes adverse effects that were reported in each clinical trial. Of the eighteen total clinical trials: four observed no adverse reactions, nine observed mild reactions, and the remaining five did not report adverse effects. Of note, none of the clinical trials observed "severe" long-term complications. Mild adverse reactions reported include localized pressure, pain, swelling, tenderness. In one study, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia were also observed. In many cases, mild post-injection symptoms were observed and only lasted a few minutes to days.

The longest duration of adverse effects was observed in a study by Sampson, Reed, Silvers, Meng, & Mandelbaum, who reported modest pain and swelling that persisted up to 1-week after injection. Analysis of the type of PRP (see Appendix A, Table 4) reveals that this study was the only study that used bovine thrombin and calcium chloride ($CaCl_2$) in the final

product. This finding suggests that the addition of either bovine thrombin or $CaCl_2$ to the final product may contribute to adverse effects of PRP injections. Similarly, Filardo et al., (2012a), Filardo et al. (2015), and Gormeli et al. (2017) observed similar mild adverse reactions with the use of $CaCl_2$. Patel, Dhillon, Aggarwal, Marwaha, & Jain, (2013) also used $CaCl_2$ and observed higher incidence of adverse reactions in patients that received two injections compared to a single injection. This further supports that $CaCl_2$ may contribute to adverse reactions. Contrarily, Kon et al. (2011) observed no adverse reactions with the addition of $CaCl_2$. The use of other types of activation factors are questionable in contributing to adverse effects. Lisi (2018) used calcium gluconate with no observed adverse reactions. Gobbi, Lad, & Karnatziko (2015) was the only clinical trial that used collagen or Von Willebrand factor and did not report adverse reactions.

Regarding platelet concentration, Filardo et al. (2012a) observed mild adverse effects in patients treated with PRP (Double spin) compared to PRGF (Single Spin), suggesting that higher platelet concentration may attribute to adverse effects. This trend was also noted in Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) whom concluded that the adverse effects of PRP may be closely related with concentration of platelets. Due to lack of reported platelet concentrations within selected studies, there was limited supporting data to strengthen the argument that the platelet concentration affected outcomes for adverse reactions.

Regarding leukocyte concentration, there was limited available data to make to support the argument that leukocyte concentration attributes to adverse effects. The PRP used in Filardo et al. (2012a), Filardo et al. (2012b), and Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh (2012) were assumed to have used LR-PRP. In each of these studies, mild adverse effects were noted. This may suggest that high leukocyte content may attribute to adverse effects. Similarly,

Filardo et al. (2012b) concluded that adverse reactions may be due to the high leukocyte content. Although adverse events seem to be more prevalent in preparations with leukocytes, Kon et al. (2011), whom also used LR-PRP, observed no adverse reactions. Due to the lack of defined parameters of PRP classification and lack of adverse events, there was inconsistent evidence to support the theory that high leukocyte number or concentration contributed to post-injection symptoms.

Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) suggested that the amount of anticoagulant within PRP preparation may attribute to adverse effects. Under review of the methods of preparation, it was noted that most studies used anticoagulant including sodium citrate, citrate phosphate dextrose and adenine, and citrate dextrose-A. In other studies, the type of anticoagulant was not disclosed. Only Cole, Karas, Hussey, Pilz, & Fortier (2017) and Smith (2016) did not definitively use anticoagulant. The former did not report adverse reactions while the latter observed no adverse reactions. Due to the extensive use of anticoagulant in studies and limited report of the type of anticoagulant used, there was inconsistent evidence to support the idea that anticoagulants contribute to adverse reactions.

Trends in Efficacy

WOMAC and Analysis**.** For the scope of this review, the WOMAC index was used as the main parameter to evaluate clinical efficacy. Due to the wide variety of different outcome scales and parameters used to assess the clinical data in comprehensive review, only a select few studies were able to be comparatively analyzed. Appendix B, Table 7-10, summarizes the WOMAC measurements at baseline and as percent change form baseline at respective follow-up periods. Also, variability in the number of doses, cycles, and volumes of injection were analyzed (Appendix B, Table 11 and 12) along with the type of PRP (Appendix A, Table 4 and 5) to

evaluate trends in efficacy.

PRP Preparation Considerations. In the studies under review, there were a few important variables to consider, including: the differences in the total whole blood drawn, division of the blood depending on number of injections to be administered, and the final product volume after filtration and separation methods were applied. The initial total blood volume drawn ranged from 14-150 mL. In addition, there was an appreciable difference in final product ranging from 2-8 mL for each injection. There were no obvious trends or correlations regarding efficacy that could be extrapolated given the available data on the above three variables.

Only a few studies were able to evaluate platelet concentration and leukocytes effect on efficacy. Cole, Karas, Hussey, Pilz, & Fortier (2017) suggested that higher concentrations of PRP did not correlate with clinical outcomes. Similarly, Filardo et al. (2012a) compared PRGF (single spin) to PRP (double spin) suggested that there was no difference in clinical efficacy regarding platelet concentration or presence or absence of leukocytes within the final PRP product. Filardo et al. (2015) did not find any correlation regarding efficacy involving platelet concentration of PRP administered. Rayegani et al. (2013) also concluded that platelet concentration may not contribute to the efficacy of PRP. These findings suggest that there may not be any correlation regarding clinical efficacy when it comes to the concentration of platelets or leukocytes.

Symptoms and Time Considerations. Regardless of the variety of scales and parameters used in the many clinical studies reviewed, almost all studies showed improvements in the clinical symptoms of pain, stiffness, and function as compared to baseline. Smith (2016) observed that patients who received LP-PRP had significant improvement in WOMAC scores compared to baseline, concluding that LP-PRP reduces osteoarthritic related pain and stiffness

improving physical function of the knee. In addition, Cole, Karas, Hussey, Pilz, & Fortier (2017) observed statistically significant improvement in pain and function from baseline with PRP. Lisi et al. (2018) also mentioned that activated PRP may improve function and quality of life. Kon et al. (2011) stated that PRP is effective in treatment of OA. As many studies used subjective outcome measurements, it was interesting to find the study by Lisi et al. (2018) utilized more objective measurements with MRI imaging of the knee at the end of the study. Interestingly, there was an observed reduction of articular damage at six months, which suggest PRP may promote underlying chondral tissue healing.

Reported beneficial effects appeared to start within the first couple of weeks of injection. Smith (2016) suggested that effects began one week after the first injection. Cerza et al. (2012) suggested that the beneficial effects are seen within four weeks of injection. The length of beneficial effects in each study was evaluated in comparison to dose and total number of injections. However, as previously mentioned, only a few studies were able to be analyzed using WOMAC. Figure 1-4 depicts global WOMAC and WOMAC sub-scales for respective studies as percent change from baseline.

Figure 1

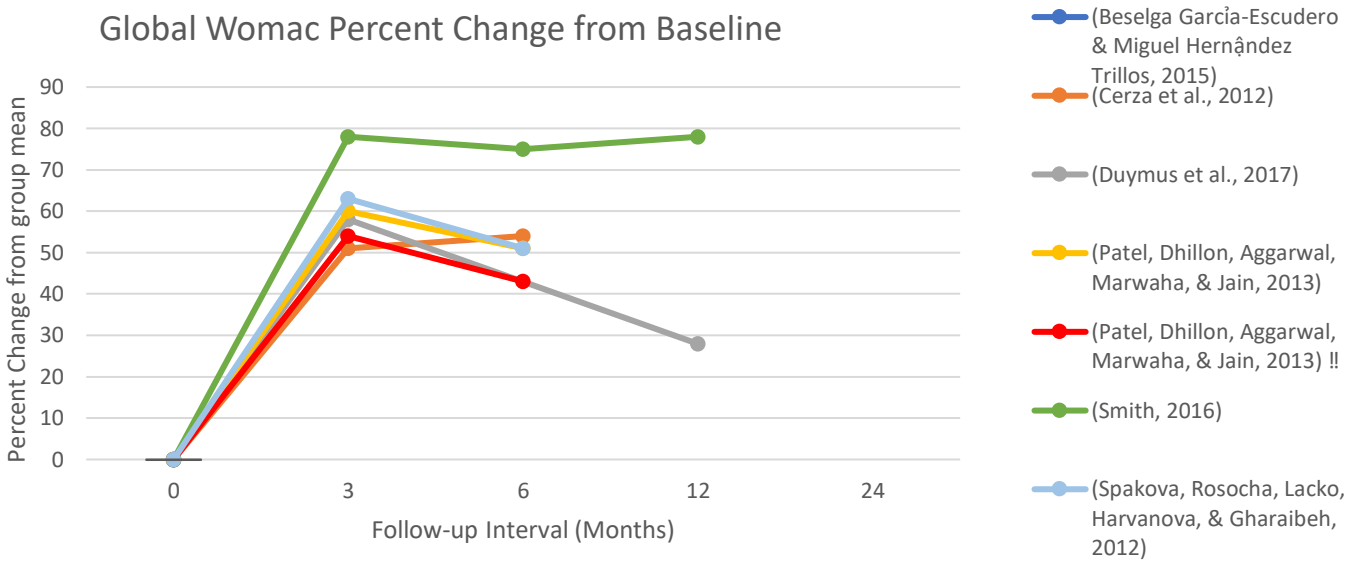


Figure 2

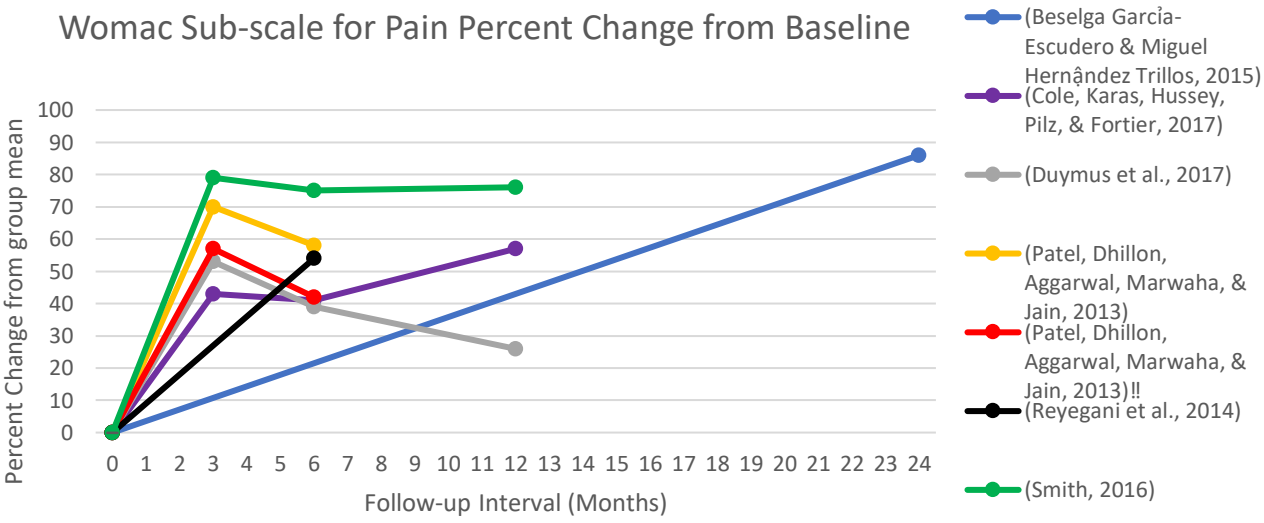


Figure 3

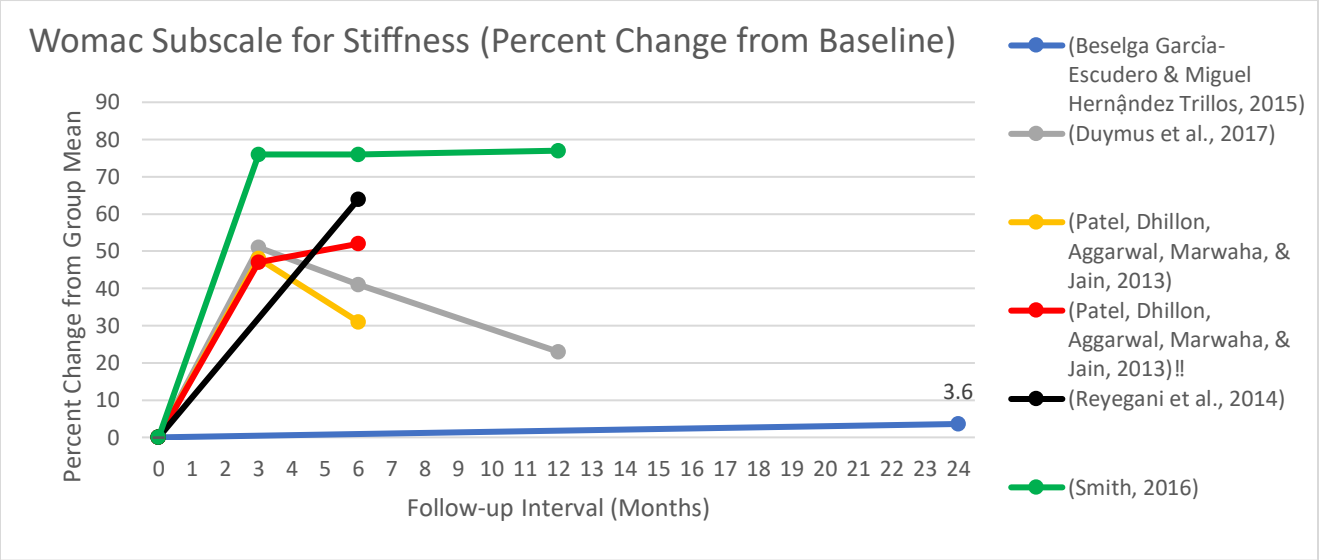
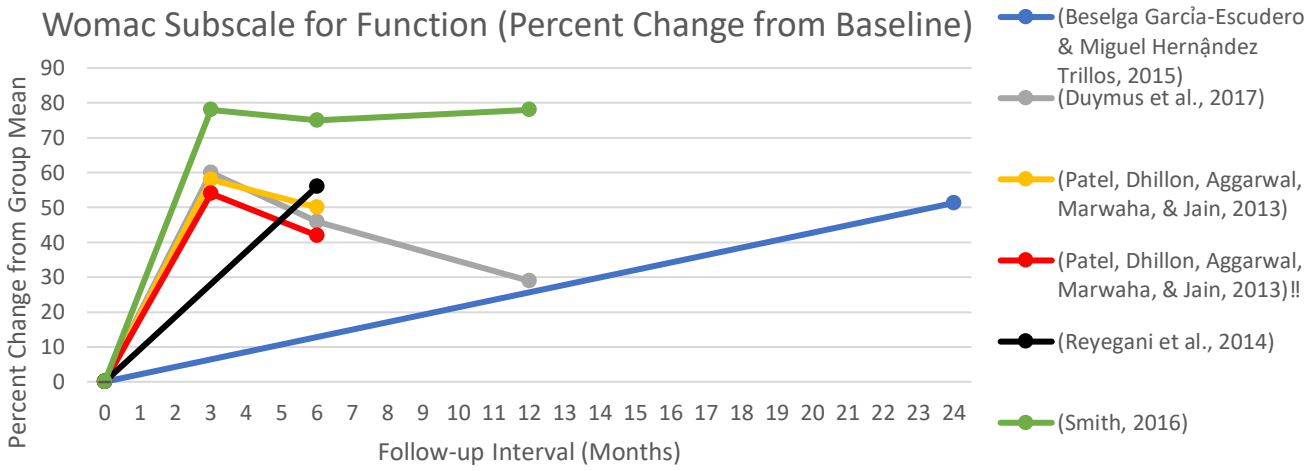


Figure 4



Disappointingly, many studies only went through six months. Trends in the represented studies shows that there is improvement up to three months with a declining trend after the three-month period. Although there seems to be a decline for subsequent follow-ups beyond this time period, the WOMAC scores still show substantial improvement from baseline. There were consistent observations revealing that the beneficial effects of PRP deteriorate over time. Lisi et al. (2018) and Filardo et al. (2012b) conlcuded that activated PRPs effects may last up to one

year. The deterioration of beneficial effects seems to be sooner for those that received only one injection comparted to multiple injections over several weeks. Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) also observed that the beneficial effects seem to deteriorate after six months. Duymus et al. (2017) suggested that the effects of two injections lasted at least 12-months. Cole, Karas, Hussey, Pilz, & Fortier (2017) observed a deterioration of effects between the 24- and 52-week follow-up vists with the application of three injections at 4-week intervals. These findings seem to be consistent through many of the studies under review. Contrarily, Kon et al. (2011) observed no decline in efficacy with sustained improvement of up to 6-months.

Single versus Multiple Dose Considerations. The total number of IAI used in each study ranged from one to six injections. Only three studies, Gormeli et al. (2017), Jang, Kim, & Cha (2013), Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) used a single injection. The intervals at which IAI was performed ranged from one to four weeks. Only two studies, Baltzer, Moser, Jansen, & Krauspe (2009) and Gobbi, Lad, & Karnatziko (2015), used multiple cycles of injections.

Gormeli et al. (2017) suggests that there are superior clinical benefits from multiple injections compared to single injections of PRP. Gobbi, Lad, & Karnatziko, (2015) also conlcuded that the beneficial effects of PRP may deteriorate overtime and that cyclical application of PRP may be more efficacious at relieving pain for longer periods of time. Similarly, Duymus et al. (2017) suggests that providing sequential doses over months may be an effective therapeutic approach. Interestingly, Baltzer, Moser, Jansen, Krauspe (2009) observed that the effects of six IAI of PRP with growth factors showed sustained benefits up to two years. This further suggests that multiple injections are more efficacious than a single injection and that there may be greater improvement with the addition of concentrated growth factors.

Age Considerations. Multiple studies observed more beneficial effect in those that are young with less efficacy in patients that are older. Filardo et al. (2012a) observed a trend were better results were achieved in patients that were younger, however these results were not statistically significant. Similarly, Kon et al (2011) observed less beneficial effects in patients that are older than 50 years. Contrarily, Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) observed no correlation with age.

Osteoarthritis Severity Considerations. Although the general literature appears to still be mixed regarding the effects of PRP injection of the knee and OA severity, there is a subtle trend towards improved efficacy for mild-moderate OA as compared to severe OA. Both Filardo et al. (2012a) and Kon et al. (2011) found that there was a consistent trend with improved efficacy in and those with mild cartilage degeneration compared to those with more advanced knee OA. Contrarily, Cerza et al. (2012) did not observe any correlation between efficacy related to OA severity. Filardo et al. (2012a) found that there were favorable outcomes in all stages of OA severity (KL grade 0-4). Filardo et al. (2012b) observed trends in improvement from baseline regardless of OA severity. However, Filardo et al. (2015) failed to observe any correlation between clinical outcome and the grade of articular degeneration. Gobbi, Lad, & Karnatziko (2015) suggested that PRP can improve function and reduce pain in the early stages of OA. Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) suggest that PRP is an effective short-term option for relieving pain, stiffness, and knee function in early OA. Cole, Karas, Hussey, Pilz, & Fortier (2017) concluded that PRP may be more effective in those who have lower OA severity (KL grade I or II). Gormeli et al. (2017) suggested that there is clinical benefit for all degrees of OA severity.

Interestingly, Filardo (2012b) found that there was no major difference between single and multiple dose treatments of PRP with more advanced OA severity. Patel, Dhillon, Aggarwal, Marwaha, & Jain (2013) suggested that both single and double injections of LP-PRP alleviate symptoms of early knee osteoarthritis. Similarly, Gormeli et al. (2017) suggested that there is a greater efficacy with multiple doses of PRP compared to a single IAI PRP in patients with mild-moderate OA. There seems to be no difference in efficacy between multiple or single dose in patients with severe OA. Intuitively, it may be unnecessary to use multiple injections to treat patients with severe OA. However, analyses suggest there may be benefit from multiple injections for those with mild-moderate OA.

Body Mass Index Considerations. There were only a few studies that evaluated and observed correlation between efficacy and BMI. Of which, Cole, Karas, Hussey, Pilz, & Fortier (2017) was the only study that suggested that PRP may be more effective in those who are of healthy weight (BMI 18.5-24).

PRP and Exercise Considerations. There were three studies that allowed or made therapeutic exercise mandatory. Through analysis of these studies, exercise was a major influence on the clinical outcomes for efficacy. Even though, there is clear benefit with therapeutic exercise, evaluation of exercise alone was beyond the scope of this review. Rayegani et al. (2013) concluded that PPR in combination with therapeutic exercise can be more effective in reducing pain and stiffness and improving quality of life compared to therapeutic exercise alone. Similarly, Beselga Garcıa-Escudero & Miguel Hernậndez Trillos (2015) suggested that four IAI of PRP at 1-week intervals, in addition to therapeutic exercise, may provide sustained improvement of pain and physical function for up to 2 years. This study also concluded that ACS with physiotherapy is an effective treatment for OA of the knee regardless of severity. Gobbi,

Lad, & Karnatziko (2015) observed similar trends with patients that were involved in recreational sports.

Concentrated Growth Factor Considerations. A study conducted by Baltzer, Moser, Jansen, Krauspe (2009) evaluated PRP with IL-1Ra and therapeutic exercise. Although there were no comparable studies to evaluate the efficacy with the addition of concentrated growth factors, this study is worthy of mention. This study concluded that PRP with the addition of growth factors (Orthokine) may improve pain and physical function. This suggests that the addition of different cytokines along with PRP may further improve efficacy.

AAOS and Clinical Practice Guidelines

In respect to the 2013 AAOS guidelines, there were similar biases and questionable study strengths to argue different recommendations for the use of PRP for the knee. However, there were only three studies that were analyzed to support these recommendations. Only one study (Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh (2012)) overlapped with the literature that was used in this review. Therefore, there is a need to revisit the current literature on the efficacy of PRP for the treatment of OA of the knee. Future recommendations for other nationally recognized organizations may be benefit from articles discussed in this literature review. A summary of study comparisons and designs are listed in Appendix C.

Conclusion

In this review there were many studies that had poor study design, low strength, and different outcome measurements. Also, the diverse nature of PPR preparation made analyzing its clinical efficacy difficult. The unavoidable truth is that the use of PRP lacks standardization of methods of preparation, classification, number of doses or cycles, and time frame for subsequent

doses. However, there may yet be statistically significant trends in current literature that may influence future clinical practice guideline recommendations.

Current literature suggests that, IAI of PRP for osteoarthritis of the knee has a very low rate of severe complications. Although there is suggested to be an increase in observed adverse effects compared to placebo, reactions seem to be only mild; local injection site problems and vasovagal symptoms very short in duration. There seems to be a correlation with higher incidence of adverse events in preparations that have higher concentration of platelets or in preparations that used $CaCl_2$ or bovine thrombin for activation. There was limited evidence to suggest that anticoagulant or the presence of white blood cells attributed to adverse reactions. However, many studies suggested that adverse reactions may be related to the activation of inflammatory cascades. Therefore, LP-PRP preparations should be used without activators to minimize such adverse reactions.

There is evidence that suggests PRP is effective in relieving symptoms of OA related pain, stiffness, and function. The beneficial effects may be first noticed within a few weeks after injection and are sustained up to months to years in some cases. However, the benefits of PRP have consistently shown to deteriorate over time, often over several months. Contrarily, cyclical injections provide sustained benefit for longer-term. Cyclical injections may be more beneficial in those with mild-moderate cartilage degeneration compared to those with more sever manifestations of OA. Some studies suggest that LP-PRP may have a greater effect on functional outcome scores than LR-PRP. However, analysis of studies in this review does not support the same conclusion. Also, trends in efficacy appear to be more substantial for those who are young and those with less severity cartilage degeneration. However, there is still marked improvement from base-line symptoms for patients who are older with more advanced osteoarthritis.

Limitations

Study comparisons were difficult given the lack of consistent study designs throughout the comprehensive review. Some of these frustrating inconsistencies included: platelet separation techniques, variety of measurement scales and indexes, and overwhelming bias. Independent statistical analysis of alternative outcome measurements were time prohibitive and were not completed.

For certain, the variety of outcome measurement scales used between studies limited this review's strength. Due to the use of different outcome measurements, it was difficult to evaluate and compare efficacy between studies. Therefore, primary comparisons in this review were assessed by percentage of improvement from baseline. Also, only the studies that used WOMAC scores as an outcome measurement with disclosed data were compared. As discussed previously, final PRP product may vary greatly and is depends on many factors. Therefore, trends that are suggested within graphic representation Figure 1-4 should be analyzed with the method of PRP preparation in mind. Also, the follow-up time periods were not consistent between studies. Some studies started their follow-up protocols immediately after the first injection was given while others recorded post-injection improvement time after administering the last injection of the multidose protocol. Therefore, it was difficult to truly assess length of therapeutic benefit.

Sample size, age, and severity of OA also had a wide range of variability. There were a few cohort studies that had limited sample sizes. Also, the age-range of each study was highly variable. Multiple studies had age ranges from 18 to 90 years old. The results of these studies would be more beneficial if raw data was disclosed because as mentioned above age was considered a major contributor to the efficacy of PRP. In the same respect, OA severity also may contribute to bias. Most studies use the Kellgren and Lawrence system to grade OA severity,

however, two other grading systems were used in various studies which made comparisons between studies difficult or not possible. Also, the studies that consisted of higher or lower grades of severity may contribute to bias if the author did not analyze correlations of efficacy with OA severity.

Overall, there were many biases that may limit the strength of findings suggested in the selected literature. The classification of the type of PRP that was used in each study was difficult to evaluate if it was not discussed in detail. Whether or not leukocytes were present in the final product was a major limitation of most clinical trial in this review. Ideally, studies should disclose platelet and white blood cell concentration, anticoagulant, activation methods to aid in differentiating the optimal final product.

Recommendations for Future Research

It was disappointing to find that some clinical trials did not record or report adverse events that were observed, and this weakened the analysis of meaningful trends. Future studies should report all adverse effects and aim to define parameters of inclusion for adverse events. Many studies do not quantify cellular components to allow accurate comparison between studies and the effects of platelet concentration and presence or absence of leukocytes. Rayegani et al. (2013) had a study design that sampled the final PRP product to evaluate the platelet concentration and WBC count. Similar laboratory evaluation may be of great benefit for future studies in evaluating the optimal preparation of PRP.

The mechanism of PRP's beneficial effects of is widely known. Whether these effects stem form purely anti-inflammatory effects and/or healing through cellular signaling to promote proliferation and remodeling of chondral tissue is an area of interest. Cole, Karas, Hussey, Pilz, & Fortier (2017) observed a downward trend in the amount of pro-inflammatory cytokines in

knees that were treated with LP- PRP. This study suggests that the proposed anti-inflammatory properties of PRP may contribute to improvement of OA symptoms. Future studies should also focus on more objective measurement outcomes such as synovial fluid analysis of biochemical markers or MRI imaging to obtain more solid evidence to support proposed theories for the mechanism of action. Also, the use of growth factors is a growing area of interest in the field of regenerative medicine. Whether or not isolated growth factors in combination with PRP has clear benefits compared to PRP alone, future studies comparing PRP to PRP with isolated growth factors may show promise.

Applicability to Clinical Practice

There are several options to consider when determining the appropriate method of treatment for knee OA. Initial treatment of knee OA should be made on an individual basis and should include physical therapy, exercise, diet, as well as other pharmacologic and non-invasive modalities. Non-invasive therapeutic options should be utilized before considering any type of intra-articular injection. In those that fail traditional therapeutic management, the addition of PRP to other non-invasive modalities may be a great option for those wanting to delay or avoid joint replacement surgery. The financial aspect may also play a major role for those considering PRP; the cost of PRP can range from $400-1500 with discounted rates for multiple or bilateral injections. Disappointingly, there is currently no insurance coverage for PRP injections, except for special circumstances involving workman's compensation or motor vehicle insurances.

The clinical application of PRP is generally straight forward and has the capability to be prepared and administered in an outpatient setting. Preparation time is usually less than an hour and product can be refrigerated for future injections. Clinicians should keep in mind that the current literature suggests that there is more benefit for those who are younger with mild to

moderate osteoarthritis of the knee. Also, PRP injections are less effective in those that are older with more severe manifestations of knee osteoarthritis. Multiple injections seem to have longer lasting benefits compared to a single injection, especially in those with mild-moderate osteoarthritis. Patients that are treated with antiplatelet medications should not receive PRP injections because these medications may inhibit or interfere with the platelet function and decrease efficacy. As the application of PRP is still in its infancy, clinicians implementing PRP injections for OA of the knee should be expected to make changes in the method of preparation and administration in years to come as more clinical trials aim to improve safety and efficacy of PRP and define optimal preparation methods.

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Appendix A

Adverse Effects by Study

Table A3

Study	Reported Adverse Effects
(Baltzer, Moser, Jansen, & Krauspe, 2009)	Localized pressure, pain, swelling, tenderness, and heat that lasted up to 2 days
(Beselga Garcỉa-Escudero & Miguel Hernậndez Trillos, 2015)	No severe adverse effects
(Cerza et al., 2012)	No observed adverse reactions
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	†
(Duymus et al., 2017)	†
(Filardo et al., 2012a)	No severe adverse events observed. Transient pain and swelling in both groups with more incidence in double spin group
(Filardo et al., 2012b)	Minor events. Mild pain and effusion
(Filardo et al., 2015)	Transient post injection pain and swelling.
(Gobbi, Lad, & Karnatziko, 2015)	†
(Gormeli et al., 2017)	‡
(Jang, Kim, & Cha, 2013)	†
(Kon et al, 2011)	No observed adverse reactions
(Lisi, 2018)	No side-effects observed
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	Syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia. Higher incidence in those that received 2 injections
(Reyegani et al., 2014)	Transient local pain and swelling with no significant complications
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	There was modest pain persisting 1-week after injection with no long-term complications.
(Smith, 2016)	No observed adverse reactions
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	Mild pain which resolved after 2 days with no severe adverse events

†= Not discussed. ‡=Not discussed but has outcome measurement for adverse events

Appendix A

Study Specific PRP Preparation

Table A4

Study	# Spins	Spin 1 (speed, min)	Spin 2 (speed, min)	Spin 3 (Speed, min)	Comments
(Baltzer, Moser, Jansen, & Krauspe, 2009)	1	†	Na	Na	IL-1Ra was added to final product. Platelets were frozen for subsequent injections
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	1	3000 G, 10	Na	Na	Platelets incubated 37 degrease Celsius for 6 hours, filtered, then frozen for subsequent injections
(Cerza et al., 2012)	†	†	†	†	preparation not discussed
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	1	1500 rpm, 5	Na	Na	
(Duymus et al., 2017)	1	3700 rpm, 7	Na	Na	Platelets may have been frozen (not specified) for subsequent injections
(Filardo et al., 2012a)	1	580 rpm, 8	Na	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2012a)!!	2	1800 rpm, 15	2500 rpm, 10	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2012b)	2	1480 rpm, 6	3400 rpm, 15	Na	Platelets were frozen for subsequent injections
(Filardo et al., 2015)	2	1480 rpm, 6	3400 rpm, 15	Na	Platelets were frozen for subsequent injections
(Gobbi, Lad, & Karnatziko, 2015)	1	3500 rpm, 5	Na	Na	Prolonged cycles of PRP were injected (1 IAI per month/ 3-month interval).
(Gormeli et al., 2017)	2	1500 rpm, 6	3500 rpm, 12	Na	Platelets were frozen for subsequent injections
(Jang, Kim, & Cha, 2013)	†	†	†	†	Magellen autologous platelet separator
(Kon et al, 2011)	2	1480 rpm, 6	3400 rpm, 14	Na	Platelets were frozen for subsequent injections
(Lisi, 2018)	1	900 rpm, 7 min	Na	Na	Leukocyte removal was not discussed
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	1	1500 rpm, 15	Na	Na	Leukocytes removed with filter
(Reyegani et al., 2014)	2	1600 rpm, 15	2800 rpm, 7	Na	
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	1	1700 G, 15	Na	Na	Platelets may have been frozen (not specified) for subsequent injections
(Smith, 2016)	1	1500 rpm, 5	Na	Na	Leukocytes removed with filter
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	3	3200 rpm, 15	1500, 10	3200, 10	

Rpm- revolutions per minute. G= g-force. Na= Not applicable. †= Insufficient data. !!= 2nd ACS group in study

Appendix A

PRP Classification by Study

Table A5

Study	Classification	Anticoagulant	Activation
(Baltzer, Moser, Jansen, & Krauspe, 2009)	LP-PRP or LR-PRP* with IL-1Ra	Yes†	‡
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	LP-PRP* or LR-PRP*	Yes†	No
(Cerza et al., 2012)	LP-PRP	Sodium citrate	‡
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	LP-PRP	No	No
(Duymus et al., 2017)	LP-PRP	Yes†	‡
(Filardo et al., 2012a) !!	PRGF (LP-PRP*) and LR-PRP	Yes†	CaCl2
(Filardo et al., 2012b)	LR-PRP	Yes†	‡
(Filardo et al., 2015)	LP-PRP or LR-PRP*	Yes†	CaCl2
(Gobbi, Lad, & Karnatziko, 2015)	LP-PRP	‡	Collagen or Von Willebrand Factor
(Gormeli et al., 2017)	LP-PRP or LR-PRP*	Sodium citrate	CaCl2
(Jang, Kim, & Cha, 2013)	LP-PRP or LR-PRP*	ACD-A	No
(Kon et al, 2011)	LR-PRP*	Yes†	CaCl2
(Lisi, 2018)	LP-PRP*	ACD-A	Calcium gluconate
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	LP-PRP*	CPD-A1	CaCl2
(Reyegani et al., 2014)	LR-PRP	ACD-A	No
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	LP-PRP*	ACD-A	Bovine thrombin + CaCl2
(Smith, 2016)	LP-PRFM	No	No
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	LR-PRP*	Sodium citrate	No

PRP=Platelet-Rich Plasma, PRFM= Platelet-Rich Fibrin Matrix PRGF= Plasma Rich in Growth Factors, LP= Leukocyte-Poor, LR= Leukocyte-Rich

CPD-A1= Citrate Phosphate Dextrose and Adenine, ACD-Citrate dextrose-A, IL-1Ra=interleukin-1 Receptor Agonist

*= Defined through analysis of reported preparation method with assistance from Dr. Launchbury

† =assumed from preparation method. ‡= Unknown; not enough information. !!= Study has 2 types of ACS

Appendix B

Table B6. Study Outcomes Measured

	Study Outcome Measured											
Study	WOMAC(g)	WOMAC(p)	WOMAC(s)	WOMAC(f)	IKDC	VAS	EQ-VAS	KOOS	Tenger	Satisfaction	Adverse Events	OTHER
(Baltzer, Moser, Jansen, & Krauspe, 2009)	X	X	X	X		X				X	X	
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	X	X	X	X							X†	NRS
(Cerza et al., 2012)	X	X	X	X							X†	
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)		X			X	X						Synovial fluid analysis (Pro-Inflammatory Cytokines)
(Duymus et al., 2017)	X	X	X	X		X						
(Filardo et al., 2012a)					X		X		X	X	X	
(Filardo et al., 2012b)					X		X	X	X	X	X	ROM, Knee circumference changes
(Filardo et al., 2015)					X		X	X	X	X	X	ROM, Trans Patellar circumference changes
(Gobbi, Lad, & Karnatziko, 2015)						X		X	X			Marx score
(Gormeli et al., 2017)					X		X				X‡	
(Jang, Kim, & Cha, 2013)					X	X						
(Kon et al, 2011)					X		X			X	X	
(Lisi, 2018)	X	X	X	X		X			X		X†	AKSS, Lysholm, Lequesne, MRI
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	X	X	X	X		X				X	X	
(Reyegani et al., 2014)	X	X	X	X							X†	SF-36, QOL
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)						X		X		X	X†	US (cartilage thickness)
(Smith, 2016)	X	X	X	X							X	
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	X	X	X	X							X†	NRS

WOMAC= Western Ontario and McMaster universities Osteoarthritis Index. WOMAC(g)=Global WOMAC, WOMAC(p)= WOMAC subscale for pain, WOMAC(s)=WOMAC subscale for stiffness, WOMAC(f)=WOMAC subscale for physical function, IKDC= International Knee Documentation score, VAS= Visual analogue scale, EQ-VAS= EuroQol-Visual analogue scale, KOOS= Knee Injury and Osteoarthritis Outcome Score, Tegner= Tegner activity level scale, AKSS= American Knee Society Score, Lysholm knee scoring scale, Lequesne= Lequesne Algo-functional index, NRS= Numeric Rating Scale, SF-36= Short Form 36, QOL=Quality of Life, US=Ultra sound, MRI= Magnetic Resonance Imaging, ROM=Range of Motion

†= Discussed but not a designated outcome measurement. ‡ = Not discussed, but had designated outcome measurement

Appendix B

Global WOMAC (Percent Change from Baseline)

Table B7

		Follow-up interval (months)			
Study	Baseline (Group Mean)	3	6	12	24
(Baltzer, Moser, Jansen, & Krauspe, 2009)	¥	¥	¥	¥	¥
(Beselga Garcia-Escudero & Miguel Hernåndez Trillos, 2015)	0(81.6)	¥	¥	¥	56.9
(Cerza et al., 2012)	0(79.6)	51	54	¥	¥
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	†	†	†	†	†
(Duymus et al., 2017)	0(76.1)	58	¥	28	¥
(Filardo et al., 2012a)	†	†	†	†	†
(Filardo et al., 2012b)	†	†	†	†	†
(Filardo et al., 2015)	†	†	†	†	†
(Gobbi, Lad, & Karnatziko, 2015)	†	†	†	†	†
(Gormeli et al., 2017)	†	†	†	†	†
(Jang, Kim, & Cha, 2013)	†	†	†	†	†
(Kon et al, 2011)	†	†	†	†	†
(Lisi, 2018)	‡	‡	‡	‡	‡
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	0(49.86)	60	51	¥	¥
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013) !!	0(53.2)	54	43	¥	¥
(Reyegani et al., 2014)	‡	‡	‡	‡	‡
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	†	†	†	†	†
(Smith, 2016)	0(47)	78	75	78	¥
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	0(38.76)	63	51	¥	¥

†=Outcome not measured. ¥=Outcome not measured for this time interval. ‡=Lack of raw data. !!=Second group in study.

Note: Data under "Follow-up interval" is expressed as negative percent change from baseline.

Appendix B

WOMAC Subscale for Pain (Percent Change from Baseline)

TABLE B8

		Follow-up interval (months)			
Study	Baseline (Group Mean)	3	6	12	24
(Baltzer, Moser, Jansen, & Krauspe, 2009)	¥	¥	¥	¥	¥
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	0(17.9)	¥	¥	¥	86
(Cerza et al., 2012)	‡	‡	‡	‡	‡
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	0(7)	43	41	57	¥
(Duymus et al., 2017)	0(15.4)	53	39	26	¥
(Filardo et al., 2012a)	†	†	†	†	†
(Filardo et al., 2012b)	†	†	†	†	†
(Filardo et al., 2015)	†	†	†	†	†
(Gobbi, Lad, & Karnatziko, 2015)	†	†	†	†	†
(Gormeli et al., 2017)	†	†	†	†	†
(Jang, Kim, & Cha, 2013)	†	†	†	†	†
(Kon et al, 2011)	†	†	†	†	†
(Lisi, 2018)	‡	‡	‡	‡	‡
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	0(10.18)	70	58	¥	¥
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013) !!	0(10.62)	57	42	¥	¥
(Reyegani et al., 2014)	0(9.13)	¥	54	¥	¥
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	†	†	†	†	†
(Smith, 2016)	0(10)	79	75	76	¥
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	‡	‡	‡	‡	‡

†=Outcome not measured. ¥=Outcome not measured for this time interval. ‡=Lack of raw data. !!=Second group in study.

Note: Data under “Follow-up interval” is expressed as negative percent change from baseline.

Appendix B

WOMAC Subscale for Stiffness (Percent Change from Baseline)

Table B9

		Follow-up interval (months)			
Study	Baseline (Group Mean)	3	6	12	24
(Baltzer, Moser, Jansen, & Krauspe, 2009)	¥	¥	¥	¥	¥
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	0(3.4)	¥	¥	¥	3.6
(Cerza et al., 2012)	‡	‡	‡	‡	‡
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	¥	¥	¥	¥	¥
(Duymus et al., 2017)	0(6.1)	51	41	23	¥
(Filardo et al., 2012a)	†	†	†	†	†
(Filardo et al., 2012b)	†	†	†	†	†
(Filardo et al., 2015)	†	†	†	†	†
(Gobbi, Lad, & Karnatziko, 2015)	†	†	†	†	†
(Gormeli et al., 2017)	†	†	†	†	†
(Jang, Kim, & Cha, 2013)	†	†	†	†	†
(Kon et al, 2011)	†	†	†	†	†
(Lisi, 2018)	‡	‡	‡	‡	‡
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	0(3.12)	48	31	¥	¥
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013) !!	0(3.5)	47	52	¥	¥
(Reyegani et al., 2014)	0(2.3)	¥	64	¥	¥
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	†	†	†	†	†
(Smith, 2016)	0(4)	76	76	77	¥
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	‡	‡	‡	‡	‡

†=Outcome not measured. ¥=Outcome not measured for this time interval. ‡=Lack of raw data. !!=Second group in study.

Note: Data under “Follow-up interval” is expressed as negative percent change from baseline.

Appendix B

WOMAC Subscale for Function (Percent Change from Baseline)

Table B10

		Follow-up interval (months)			
Study	Baseline (Group Mean)	3	6	12	24
(Baltzer, Moser, Jansen, & Krauspe, 2009)	¥	¥	¥	¥	¥
(Beselga Garcia-Escudero & Miguel Hernậndez Trillos, 2015)	0(60.4)	¥	¥	¥	51.3
(Cerza et al., 2012)	‡	‡	‡	‡	‡
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	¥	¥	¥	¥	¥
(Duymus et al., 2017)	0(54.5)	60	46	29	¥
(Filardo et al., 2012a)	†	†	†	†	†
(Filardo et al., 2012b)	†	†	†	†	†
(Filardo et al., 2015)	†	†	†	†	†
(Gobbi, Lad, & Karnatziko, 2015)	†	†	†	†	†
(Gormeli et al., 2017)	†	†	†	†	†
(Jang, Kim, & Cha, 2013)	†	†	†	†	†
(Kon et al, 2011)	†	†	†	†	†
(Lisi, 2018)	‡	‡	‡	‡	‡
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	0(36.56)	58	50	¥	¥
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013) !!	0(39.1)	54	42	¥	¥
(Reyegani et al., 2014)	0(‡)	¥	56	¥	¥
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	†	†	†	†	†
(Smith, 2016)	0(32)	78	75	78	¥
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	‡	‡	‡	‡	‡

†=Outcome not measured. ¥=Outcome not measured for this time interval. ‡=Lack of raw data. !!=Second group in study.

Note: Data under "Follow-up interval" is expressed as negative percent change from baseline.

Appendix B

Dose, Cycle, and Time Intervals

TABLE B11

Study	Total IAI	# IAI (at each interval)	IAI Interval (weeks)	# Cycles	Cycle Interval (weeks)
(Baltzer, Moser, Jansen, & Krauspe, 2009)	6	2	1	3	‡
(Beselga Garcia-Escudero & Miguel Hernández Trillos, 2015)	4	1	1	NA	NA
(Cerza et al., 2012)	4	1	1	NA	NA
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	3	1	1	NA	NA
(Duymus et al., 2017)	2	1	4	NA	NA
(Filardo et al., 2012a)	4	1	3	NA	NA
(Filardo et al., 2012b)	3	1	1	NA	NA
(Filardo et al., 2015)	3	1	1	NA	NA
(Gobbi, Lad, & Karnatziko, 2015)	3	1	4	NA	NA
(Gobbi, Lad, & Karnatziko, 2015) !!	3	1	4	2	4
(Gormeli et al., 2017)	1	1	Na	Na	Na
(Gormeli et al., 2017) !!	3	1	1	Na	Na
(Jang, Kim, & Cha, 2013)	1	1	Na	Na	Na
(Kon et al, 2011)	3	1	2	Na	Na
(Lisi, 2018)	3	1	4	Na	Na
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	1	1	Na	Na	Na
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	2	1	3	Na	Na
(Reyegani et al., 2014)	2	1	4	Na	Na
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	3	1	4	Na	Na
(Smith, 2016)	3	1	1	Na	Na
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	3	1	1	Na	Na

‡= insufficient data. Na= Not applicable. !!= 2nd group in study

Appendix B

Blood and Final Product Volume

TABLE B12

Study	Blood Volume (mL)		
	Whole Blood	Divided	Final product
(Baltzer, Moser, Jansen, & Krauspe, 2009)	50	6 -8	2
(Beselga Garcia-Escudero & Miguel Hernȧndez Trillos, 2015)	†	10	2
(Cerza et al., 2012)	†	12	5.5
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	†	10	4
(Duymus et al., 2017)	14	6-8	3-4
(Filardo et al., 2012a)	36	9	5
(Filardo et al., 2012a)!!	150	20	5
(Filardo et al., 2012b)	150	20	5
(Filardo et al., 2015)	150	20	5
(Gobbi, Lad, & Karnatziko, 2015)	†	8	4
(Gormeli et al., 2017)	150	20	5
(Jang, Kim, & Cha, 2013)	54	6	3
(Kon et al, 2011)	150	20	5
(Lisi, 2018)	†	20	†
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	100	50	8
(Reyegani et al., 2014)	35-40	Na	4-6
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	54	‡	6
(Smith, 2016)	†	15	3-8
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	27	9	3

†= Insufficient data. ‡=Unknown; not enough information. Na= Not applicable. !!=2nd group in study.

Appendix C

Study Design

Table C13

Study	Year	Comparison	Controlled	Randomized	Blinded
(Baltzer, Moser, Jansen, & Krauspe, 2009)	2009	IL-Ra + PRP VS HA VS Placebo	Yes	Yes	Yes
(Beselga Garcia-Escudero & Miguel Hernández Trillos, 2015)	2015	PRP + Exercise Only	No	NA*	NA*
(Cerza et al., 2012)	2012	PRP VS HA	No	Yes	No
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	2017	PRP VS HA	No	Yes	Yes
(Duymus et al., 2017)	2017	PRP VS HA VS OZONE	No	Yes	No
(Filardo et al., 2012a)	2012	PRP (Double Spin) VS PRGF (Single Spin)	No	No	No
(Filardo et al., 2012b)	2012	1 cycle PRP	No	Yes	Yes
(Filardo et al., 2015)	2015	PRP VS HMW HA	No	Yes	Yes
(Gobbi, Lad, & Karnatziko, 2015)	2015	1 Cycle PRP, 2 cycle PRP	No	Yes	No
(Gormeli et al., 2017)	2017	3 PRP VS 1 PRP VS HA VS Placebo	Yes	Yes	Yes
(Jang, Kim, & Cha, 2013)	2013	PRP and KL Grade	No	No	No
(Kon et al, 2011)	2011	PRP VS LMW HA VS HMW HA	No	Na*	No
(Lisi, 2018)	2018	PRP VS HA	No	Yes	Yes
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	2013	1 PRP VS 2 PRP VS Placebo	Yes	Yes	Yes
(Reyegani et al., 2014)	2014	2 PRP + Exercise VS Exercise Only	No	Yes	No
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	2010	PRP	No	No	No
(Smith, 2016)	2016	PRP VS Placebo	Yes	Yes	Yes
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012) ~~A~~	2012	PRP VS HA	No	Yes	No

*Not discussed in methods ~~A~~= Reviewed in AAOS 2013 guidelines for treatment of OA of the knee.

Appendix C

Study Population and Characteristics

Table C14

Study	Sample Size (N/knees)	Age range (years-years)	OA severity
(Baltzer, Moser, Jansen, & Krauspe, 2009)	378/399	40-62*	KL Grade 2-3
(Beselga Garcia-Escudero & Miguel Hernȃndez Trillos, 2015)	118/118	31-81	KL Grade 1-4
(Cerza et al., 2012)	120/120	31-90	KL Grade 1-3
(Cole, Karas, Hussey, Pilz, & Fortier, 2017)	111/111	18-80	KL Grade 1-3
(Duymus et al., 2017)	120/120	47-80	KL Grade 2-3
(Filardo et al., 2012a)	144/144	35-69*	KL Grade 0-4
(Filardo et al., 2012b)	109/109	18-80	KL Grade 0-3
(Filardo et al., 2015)	192/192	18-80 *	KL Grade 0-3
(Gobbi, Lad, & Karnatziko, 2015)	93/119	40-65	KL Grade 1-2
(Gormeli et al., 2017)	182/182	27-84	KL Grade 0-4
(Jang, Kim, & Cha, 2013)	65/90	45-75*	KL Grade 1-3
(Kon et al, 2011)	150/150	26-81	KL Grade 0-4
(Lisi, 2018)	58/62	>18	SC Grade 2-3
(Patel, Dhillon, Aggarwal, Marwaha, & Jain, 2013)	78/158	33-80	AB Grade 1-3
(Reyegani et al., 2014)	65/65	40-75*	KL Grade 1-4
(Sampson, Reed, Silvers, Meng, & Mandelbaum, 2010)	14/14	18-87	KL Grade 1-4
(Smith, 2016)	30/30	30-80	KL Grade 2-3
(Spakova, Rosocha, Lacko, Harvanova, & Gharaibeh, 2012)	120/120	19-77	KL Grade 1-3

* Estimate from article data

KL= Kellgren and Lawrence, AB= Ahlbäck grading system, SC= Shahriaree classification system