The Efficacy of Platelet-rich Plasma Injection in the Treatment of Knee Osteoarthritis: A Systematic Review

Yvonne Howell

Recommended Citation
https://commons.pacificu.edu/pa/449
The Efficacy of Platelet-rich Plasma Injection in the Treatment of Knee Osteoarthritis: A Systematic Review

Abstract

Background: Increased physical activities and prolonged life expectancies, coupled with biomechanical, metabolic, and biological changes of articular cartilage, have led to a significant rise in osteoarthritis. Unfortunately, cartilage lesions are difficult to treat because of their inherent limit of adequate blood and nerve supplies, which decreases healing potential. There are numerous, non-invasive treatment approaches with emphasis on pain management, improvement in function, and hindering the disease progress. But most of them are of short-term success with significant side effects, and do not address the biological pathology. New experimental studies have targeted the biomechanical process of OA with the focus on promoting cartilage repair or replacement. Can platelet rich-plasma (PRP) be an effective alternative option in the treatment of knee OA?

Method: An extensive search of the literature using Medline, CINAHL, Web of Science, and Google Scholar was conducted with the help of the following keywords: platelet-rich plasma, cartilage, injections, and osteoarthritis. For the purpose of performing a systematic review, articles that identified the effects of PRP injections on OA were selected and assessed via the GRADE system.

Results: Three articles were selected which directly addressed the question and met the inclusion and exclusion criteria. One prospective cohort study of 150 participants showed statistically significant improvements in pain, function and patient satisfaction with PRP treatment after 2 and 6 month follow up when compared to hyaluronic acid (HA) injections. Another cohort study of 120 individuals displayed safe and effective outcomes in pain reduction and recovery of function over HA treatments. However, major changes were only noticeable during the first 3 months. A retrospective study observed success rate of 33.3% by week 5 in the PRP group versus 10% in the control group.

Conclusion: All of the studies suggest that PRP injections are a good alternative in the treatment of OA. This procedure showed a higher degree of efficacy in pain reduction, improved function, and patient satisfaction compared to current options. No complications were identified. However, more research is needed, with emphasis on blinded randomized control trials, to further confirm current findings, determine precise mechanism of action, its disease-modifying properties, and possible long-term relief.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
platelet-rich plasma, injections, cartilage, and osteoarthritis

Subject Categories
Medicine and Health Sciences

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/449
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
The Efficacy of Platelet-rich Plasma Injection in the Treatment of Knee Osteoarthritis: A Systematic Review

Yvonne Howell

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR

For the Masters of Science Degree, August 10th, 2013

Faculty Advisor: Mark Pedemonte, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

Background: Increased physical activities and prolonged life expectancies, coupled with biomechanical, metabolic, and biological changes of articular cartilage, have led to a significant rise in osteoarthritis. Unfortunately, cartilage lesions are difficult to treat because of their inherit limit of adequate blood and nerve supplies, which decreases healing potential. There are numerous, non-invasive treatment approaches with emphasis on pain management, improvement in function, and hindering the disease progress. But most of them are of short-term success with significant side effects, and do not address the biological pathology. New experimental studies have targeted the biomechanical process of OA with the focus on promoting cartilage repair or replacement. Can platelet rich-plasma (PRP) be an effective alternative option in the treatment of knee OA?

Method: An extensive search of the literature using Medline, CINAHL, Web of Science, and Google Scholar was conducted with the help of the following keywords: platelet-rich plasma, cartilage, injections, and osteoarthritis. For the purpose of performing a systematic review, articles that identified the effects of PRP injections on OA were selected and assessed via the GRADE system.

Results: Three articles were selected which directly addressed the question and met the inclusion and exclusion criteria. One prospective cohort study of 150 participants showed statistically significant improvements in pain, function and patient satisfaction with PRP treatment after 2 and 6 month follow up when compared to hyaluronic acid (HA) injections. Another cohort study of 120 individuals displayed safe and effective outcomes in pain reduction and recovery of function over HA treatments. However, major changes were only noticeable during the first 3 months. A retrospective study observed success rate of 33.3% by week 5 in the PRP group versus 10% in the control group.

Conclusion: All of the studies suggest that PRP injections are a good alternative in the treatment of OA. This procedure showed a higher degree of efficacy in pain reduction, improved function, and patient satisfaction compared to current options. No complications were identified. However, more research is needed, with emphasis on blinded randomized control trials, to further confirm current findings, determine precise mechanism of action, its disease-modifying properties, and possible long-term relief.

Keywords: platelet-rich plasma, injections, cartilage, and osteoarthritis
Acknowledgements

[Redacted for privacy]
# Table of Contents

Biography ............................................................................................................................ 2
Abstract ............................................................................................................................... 3
Acknowledgements ............................................................................................................. 4
List of Tables ...................................................................................................................... 6
List of Abbreviations .......................................................................................................... 6
BACKGROUND ................................................................................................................ 7
METHODS ............................................................................................................................. 8
RESULTS .............................................................................................................................. 9
   Kon et al Trial .................................................................................................................... 9
   Spakova et al Trial .......................................................................................................... 11
   Sanchez et al Trial ......................................................................................................... 13
DISCUSSION ...................................................................................................................... 15
CONCLUSION .................................................................................................................... 19
References ......................................................................................................................... 21
TABLE 1 Characteristics of Reviewed Studies, GRADE profile ........................................ 23
TABLE 2 Outcome Scores for Kon et al\textsuperscript{11} .......................................................... 24
TABLE 3 Outcome Scores for Spakova et al\textsuperscript{12} ...................................................... 24
List of Tables

Table 1: Characteristics of Reviewed Studies, GRADE profile
Table 2: Outcome Score Kon et al\textsuperscript{11}
Table 3: Outcome Score Spakova et al\textsuperscript{12}

List of Abbreviations

OA..................................................................................Osteoarthritis
PRP...................................................................................Platelet-rich plasma
GF....................................................................................Growth factor
HA....................................................................................Hyaluronic acid
LW HA.................................................................Low-molecular weight hyaluronic acid
HW HA.................................................................High-molecular weight hyaluronic acid
MW HA.................................................................Medium-molecular weight hyaluronic acid
GCS........................................................................Glucocorticoid steroid
WOMAC...............................................Western Ontario and McMaster University Osteoarthritis Index
IKDC..............................................................International Knee Document Committee
EQ VAS.............................................................Visual Analogue Scale (Pain Assessment)
NRS.................................................................Numeric Rating Scale (Pain Assessment)
GRADE.......Grading of Recommendations, Assessment, Development and Evaluations
ADL........................................................................Activities of daily living
RBC........................................................................Red blood cell
WBC........................................................................White blood cell
The Efficacy of Platelet-rich Plasma Injection in the Treatment of Knee Osteoarthritis: A Systematic Review

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis afflicting mankind, especially the older population. This disease spares no race, gender, or geographical area.\textsuperscript{1,2} One of the most frequently affected joints is the knee. Osteoarthritis’s characteristic symptoms are pain, swelling, and stiffness with a decline in physical function such as walking, climbing stairs, and getting in and out of a chair. In many cases OA can be debilitating, leading to a diminished quality of life. Lawrence et al\textsuperscript{1} states that approximately 27 million Americans over the age of 25 currently suffer from OA. This number is predicted to increase by 2030 to a staggering 67 million.\textsuperscript{3} Increased physical activities as well as prolonged life expectancies, coupled with biomechanical, metabolic, and biological changes of articular cartilage, have led to a significant rise in OA. Unfortunately, articular cartilage lesions are difficult to treat because of their inherent limit of adequate blood and nerve supplies, and with that decreased healing potential.\textsuperscript{4,5} Homeostasis of extracellular matrix is impaired, inflammatory process is unavailable, and chondrocyte migration is diminished resulting in cartilage destruction, chondral bone alterations, and synovitis.\textsuperscript{6,7}

At present, there are numerous, non-invasive treatment approaches with emphasis on pain management, improvement in function and the potential to modify the disease process and progress of cartilage degeneration.\textsuperscript{5,8} Such treatment options include analgesic, steroid and non-steroid anti-inflammatory drugs, glucosamine/chondroitin
supplementation, physical therapy, and hyaluronic acid (HA) injections. However, most of them have either been of short-term success, not addressing the biological pathology or have shown only minor benefits and significant side effects.\textsuperscript{9} New experimental studies have begun to target the biomechanical process of OA with the focus on promoting cartilage repair or replacement. Particular attention has been directed toward autologous platelet-rich plasma (PRP); a high concentration of platelets suspended in a small volume of plasma after being placed in a centrifuge.\textsuperscript{6} Platelets play an essential part in tissue homeostasis. They contain a vast number of growth factors, cytokines, and bioactive proteins which help regulate tissue healing and restoration. Past studies of PRP applications have shown an increase in “cell proliferation, migration, differentiation, inflammation mediation, and matrix synthesis.” \textsuperscript{6,7}

The aim of this systematic review is to evaluate the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis.

\textbf{METHODS}

An extensive search of the literature was conducted using Medline, CINAHL, Web of Science, and Google Scholar; accessed through the Pacific University Library system. The keyword terms “platelet-rich plasma, injections, cartilage, and osteoarthritis” were searched individually and in combination. The results were limited to the English language, human subject trials, and publications since 2007. Articles that contained study designs other than randomized controlled trials (RCT), cohort studies, and case control studies were excluded. Duplicates, re-publications, descriptive reviews, and letters to the
editor were dismissed. The selected articles were analyzed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.10

RESULTS

The initial literature search yielded 23 articles that were screened for relevance to the clinical question. Five articles remained, of which 3 studies met the inclusion and exclusion criteria and were included in the systematic review. All three studies were of either prospective or retrospective cohort methodology and none were randomized control trials. Table 1 provides a summary of the studies that were included in the systematic review.

Kon et al Trial

Patient selection—The purpose of this prospective cohort study11 was to explore the effectiveness of PRP injections as a possible alternative therapy option in the treatment of knee articular cartilage degeneration. Outcomes were analyzed and compared to hyaluronic acid (HA) intra-articular injection therapy. Eligibility criteria included history of chronic knee pain or swelling (>4 months), x-ray and MRI findings of articular cartilage degeneration, and knee surgeries no less than one year prior to the start of this trial. Immunosuppressed patients and those receiving anticoagulation therapy or with a history of cardiovascular, rheumatic, and hematologic diseases were excluded. For this study, 150 patients with OA Kellgren grade 0 through IV were selected. Of those individuals, 50 were treated with PRP injections, 50 received low-molecular weight (LW HA) hyaluronic acid (molecular weight 500-730 kDa), and the rest were assigned high-molecular weight (HW HA) hyaluronic acid (molecular weight 1000-2900 kDa)
injections. Baseline characters were balanced among the single treatment group and two control groups. All participants received three injections administered every 14 days and outcomes were evaluated at 2 and 6 months post final injection. The primary outcomes of pain reduction and symptoms and function improvements were measured through the International Knee Document Committee (IKDC) and Visual Analogue Scale (EQ VAS) scoring system.\textsuperscript{11}

**Injection preparation**--PRP injections were prepared from 150ml autologous blood sample and centrifuged twice (1480rpm x 6min; 3400rpm x 15min) to separate red blood cells (RBC) and concentrate platelets. Kon et al\textsuperscript{11} states that this process resulted in a 6-fold increase in platelets when compared to whole blood. The remaining 20ml sample was divided equally into four tubes. One of the 5ml units was sent for laboratory analysis, two were stored at -30°C for future administration, and one was used immediately. Platelets were activated prior to injection using 10% calcium chloride.\textsuperscript{11}

**Outcomes**--Statistically significant improvements were noticed in all test groups with greater results in the PRP group. Evaluation of the IKDC score in the PRP group showed a steady increase from 41.2 (baseline) to 62.7 and 64.0 at 2 and 6 months follow up, respectively. Both HA groups initially increased their IKDC score by month 2, but this declined at the 6-month follow up. Baseline scores for LW HA were 44.7, then 61.7 at 2 months and 53.8 at 6 months follow up. At baseline HW HA scores were 47.3, then 54.8 and 54.0 at month 2 and 6, respectively. At the 2 months evaluation a major increase in IKDC scores was noted in the PRP and LW HA groups with lower scores in the HW HA group. However, by the 6-month follow up only the PRP group continued to show
higher scores. A separated, individual assessment of pain versus function alone was not discussed in this study in either treatment group or control groups. Further analysis showed that age was an issue in all three treatment groups with participants over the age of 50 demonstrating less improvements at 6 months follow up ($P = 0.01$). The degree of articular cartilage degeneration also seems to influence clinical outcome. Scores on the IKDC in the PRP group at 6-months follow up were higher in patients with mild OA (IKDC 74) when compared to individuals with severe OA (IKDC 46). In mild degeneration, PRP continued to increase from baseline to 6-month follow up (IKDC 41 to 60), HW HA remained stable (IKDC 48 to 53), and LW HA initially showed an increase from baseline to 2 months (IKDC 44 to 61) but this decreased at 6 months (IKDC 54). In advanced OA, PRP and LW HA decreased after a 2 months spike whereas HW HA stayed stable. Similar results were noted in the EQ VAS scoring system. No significant adverse reactions were reported during treatment and follow up. Plus, patient satisfaction in the PRP group was 82% compared to 64% in the LW HA and 66% in the HW HA.\textsuperscript{11} (See Table 2)

\textbf{Spakova et al Trial}

\textbf{Patient selection}—The second study\textsuperscript{12} reviewed focused on the safety and efficacy of PRP injections in the treatment of knee OA. Patients included in this trial had a history of continuing knee pain for 12 months, imaging findings of OA Kellgren Grade 1 through 3, and conservative therapy for the past 6 months without relief. Subjects with cofounding variables of thrombocytopenia, anemia, infections, systemic disease, and anticoagulation therapy were excluded. None of the patients enrolled received either glucocorticoid (GCS) or HA injections within 3 months of the beginning of the trial. This
prospective cohort study\textsuperscript{12} enrolled a total of 120 participants, who were randomly assigned into two equal groups of 60. Significant differences in baseline characters between these groups were not found. The treatment group received three PRP injections while the control group was treated with three 1.2% medium-molecular weight hyaluronic acid (MW HA) intra-articular visco-supplementations. Injections for both groups were administered once a week for three weeks. Follow up and evaluation occurred at 3 and 6 months post final treatment. Primary end points were measured using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and 11-point pain intensity Numeric Rating Scale (NSR) with a focus on pain reduction and function improvements.\textsuperscript{12}

\textbf{Injection preparation}--A blood sample of 27ml venous blood was dispersed into “three 10ml tubes containing 1ml of 0.106M sodium citrate.”\textsuperscript{12} The anticoagulation agent was thoroughly mixed with the blood. An aliquot was removed for laboratory analysis. The remaining blood specimen underwent three centrifugations. After the first one (3200rpm x 15min), RBC’s were separated and discarded. The second centrifugation (1500rpm x 10min) left a layer of white blood cells (WBC), which was disposed of. The third separation process (3200rpm x 10min) isolated the plasma into low and high levels of platelet concentration, with the low-levels being discarded. A 4.5-fold increase in platelets was noted after the last centrifugation. The leftover of high platelet concentrated plasma was aspirated into a 3ml syringe and administered within 30minutes of preparation. Each injection was formulated at the time of visits and none of the PRP was activated with calcium chloride.\textsuperscript{12}
Outcomes--The data analysis demonstrated a significantly better outcome in pain reduction and symptoms and function improvement in the PRP group when compared to the MW HA group. In the PRP group, the WOMAC scores initially decreased by 24.41 points at 3 months but subsequently increased by 4.50 points from the 3-month to the 6-month follow up. In addition, NRS scores were 5.27 at baseline, 2.06 at 3 months follow up, and 2.69 at the 6-month follow up, presenting a similar trend. In contrast, the MW HA control group displayed a WOMAC index decrease of 17.04 points at the 3-month evaluation and regained 4.73 points at 6 months follow up. Measurements on the NRS for the MW HA group also showed improvements, from 6.02 at baseline to 3.98 at 3-months follow up and to 4.3 at 6 month evaluation. Overall, both test groups demonstrated a noteworthy initial decrease in WOMAC and NRS scores during the first assessment at 3 months. However, both scores seem to increase at the end of the 6-month follow up. The authors claim that the result of the comparison is encouraging and that PRP may be a good treatment option. There were no other subgroup measurements such as difference in age and grade of OA, secondary outcome analysis, and separate evaluation of functional and symptoms improvement alone. No major complications were observed during this trial.12 (See Table 3)

Sanchez et al Trial

Patient selection--This observational retrospective cohort study13 was a preliminary attempt to gain insights into the effectiveness of PRP and its use for the treatment of knee OA. The authors of this study compared PRP therapy to HA intra-articular injections in patients suffering from both idiopathic and also secondary traumatic and mechanical OA. Grading and assessment for eligibility were accomplished
through radiographic imaging and patients were diagnosed with OA using the American College of Rheumatology guidelines. The article does not state whether the researchers used the Kellgren grading criteria in classifying the level of OA in their test subjects. Patients with secondary OA due to autoimmune processes, generalized OA, arthroscopic intervention in the past year and intra-articular therapy in the past 3 months prior to the start of this trial were excluded. A total of 60 patients participated in this trial with 30 individuals receiving PRP injections while the remaining participants were treated with 2% HA intra-articular treatments. The authors did not specify whether the HA injection was of low, medium, or high molecular weight. A series of three injections were provided to all the patients at one-week intervals. Evaluation was conducted at 5 weeks post final treatment, using the WOMAC scoring system for assessment. Baseline characters were matched in both groups.13

**Injection preparation**—A 34ml peripheral blood sample was obtained from the patient and dispensed into 9cc tubes containing 3.8% sodium citrate to prevent coagulation. The tubes were centrifuged only once at 640g for 8 minutes. The 2ml buffy coat and platelet concentrated plasma layer were retrieved and placed into an empty tube “under vertical air flow conditions.” Calcium chloride was added prior to administration to activate the platelets and a dosage of 6 to 8ml PRP was injected into the patient. No explanations regarding the varied doses were provided by the authors. This procedure yielded a moderate 2-fold increase in platelet concentration compared to peripheral blood.13
Outcomes—Primary outcomes were calculated “according to a reduction in WOMAC score of at least 40% from baseline” and was assessed by a blinded investigator. The article points out a potential financial bias, given the fact that three of the authors work for the company developing and selling PRP preparation kits. The study’s results reflected a significant improvement in joint pain, stiffness, and physical function in the PRP group after 5 weeks post final injection. The treatment group had a success rate of 33.3% in pain reduction. Baseline changes (P = 0.0043) in symptoms and function measurements were also noted in association to the PRP modality. The control group presented with a 10% success rate regarding pain management and positive changes from baseline (P = 0.010) in symptoms and physical function were also observed. Assessment and evaluation of symptoms and function improvements individually were not addressed. Only a few mild adverse events were observed during treatment and follow up period.

DISCUSSION

Successful treatments of articular cartilage degeneration and lesions have been difficult for most providers to achieve, and current therapeutic options have shown mixed results. The growing interests in the use of PRP in OA treatment, “which might provide cellular and humeral mediators to promote tissue healing and repair,” have gained momentum in the past few years and led to several studies. Autologous plasma is a biological therapy approach with the goal of delivering concentrated platelets to accelerate and support the healing of injuries to hard and soft tissue without exposing the patient to major risks. Growth factors, an essential part of PRP, induce differentiation of
mesenchymal stem cells into chondrocytes and thereby increase cell proliferation. They also suppress inflammatory mediators such as interleukin-1, encourage matrix deposition, and slow down catabolism.\textsuperscript{8,14} Hence, growth factors help stabilize cartilage homeostasis and possibly reverse articular degeneration. The use of autologous blood versus synthetic chemicals also eliminates the risk for allergic reaction or disease transfer in addition to limiting possible drug toxicity.\textsuperscript{15} The simple and efficient in-house preparation at the time of patient visit proves to be of advantage for the PRP procedure. However, most insurance does not cover this treatment and the cost tends to be higher for PRP than for current therapy options.\textsuperscript{16} The use of venipuncture to obtain the blood should also be considered when prescribing PRP injections.

All the studies reviewed, showed positive effects of PRP injections with improvements in symptoms and function in patients suffering from OA. Each trial demonstrated a noteworthy superiority of PRP injections when compared to HA visco-supplementation at 2 to 6-month follow up. The overall results were promising without any major procedural complications. This was especially noticeable in the younger population and with less severe OA, as observed by Kon et al.\textsuperscript{11} The fact that older and more degenerative joints tend to have less viable cells and with that a smaller potential for growth factor response, might be the reason behind the low improvements in patients over the age of 50 and with severe OA. Yet despite lower results, patients with advanced OA still benefited from PRP. Kon et al\textsuperscript{11} speculates that additional biological mechanisms not currently known, are responsible for the improvement of OA symptoms. Considering the evidence, PRP injections with their ability for biological changes to the articular cartilage may be a worthwhile treatment option.
Nonetheless, it appears that each study prepared their PRP somewhat differently. Kon et al\textsuperscript{11} separated the blood sample twice at 1480rpm x 6 minutes and again at 3400rpm x 15 minutes while Spakova et al\textsuperscript{12} used a stepwise approach of three centrifugations to concentrate the plasma (3200rpm x 15min, 1500rpm x 10min, 3200rpm x 10min). Sanchez et al\textsuperscript{13}, on the other hand, centrifuged the plasma only once at 640g x 8 minutes. Though not clearly stated, it appears that Sanchez et al\textsuperscript{13} utilized an enzyme-linked immunosorbent assay kit to quantify the amount of platelets and growth factors. In addition, Kon et al\textsuperscript{11} added calcium chloride prior to administration to activate the platelets. An anticoagulation agent was not used. Spakova et al\textsuperscript{12} did the reverse by adding sodium citrate to prevent coagulation but omitting the activation process. Sanchez et al\textsuperscript{13} opted, not only to add an anticoagulation agent, but also activate the platelets via calcium chloride. Furthermore, when measuring mean platelet concentration of PRP compared to whole blood, significant variations were noted amongst all three trials. While Kon et al\textsuperscript{11} mentioned a 600% increase in platelet concentration, Spakova et al\textsuperscript{12} and Sanchez et al\textsuperscript{13} only observed a 450% and 200% rise, respectively. Each study administered a different dose to their test subject. Kon et al\textsuperscript{11} injected 5ml of PRP, whereas Spakova et al\textsuperscript{12} administered 3ml of the tested material and Sanchez et al\textsuperscript{13} used 6 to 8ml of PRP in their injections. This leads to discussions as to whether the type of PRP preparation, injection dosage, number of platelets, and activation levels of administered PRP have an influence on the outcome.

While the studies demonstrated significant pain reduction and improvement in physical function with PRP injections, they all had their limitations. Major flaws were noted in the Sanchez et al\textsuperscript{13} trial. Specific inclusion and exclusion criteria as well as
patient selection method were poorly defined. Kellgren grading system for radiological classifications of OA was not utilized. Follow-up data was not published, making comparison to baseline measurements and outcome success impossible to validate. Publication bias with conflict of interest was present as the main authors worked for the company selling PRP preparation systems commercially. Sample size of the Sanchez et al\textsuperscript{13} trial was too small for the study’s purpose. Both, Sanchez et al\textsuperscript{13} and Spakova et al\textsuperscript{12}, did not supply confidence intervals and p-values. There is also the possibility of over- or underestimation by the patient when answering the WOMAC, IKDC, EQ VAS, or NRS questionnaires in all trials, resulting in recall bias. In general, the strength of evidence would have been more substantial had all three studies used the same, most objective outcome measurement system. The WOMAC score assessed pain, stiffness, and function and decreases were observed as the symptoms improved. The IKDC scale measured pain and ADLs and scores increased as the patients felt better. In addition, each study used a different molecular weight HA for their control group, poorly defined the molecular weight component of the chosen HA visco-supplementation, and neither article disclosed the amount of HA administered to the test subjects. None of the trials discussed loss to follow up.

To compare the pros and cons and determine the overall quality of evidence in all three studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE\textsuperscript{10}) framework was used. Despite a “very low” grade for the Spakova et al\textsuperscript{13} trial due to several limitations, this systematic review received an overall “low” GRADE rating. Any further research done to expand on the use of PRP injection in the
treatment of OA is “very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate”10.

Regardless of the “low” GRADE and limited data of the reviewed studies, it is reasonable and safe to recommend and allow patients who are curious about exploring biological and alternative therapy options for the treatment of knee OA to do so. Based on the encouraging evidence demonstrated by the three articles analyzed, practitioners should feel secure in recommending PRP injections to their patients suffering from OA, who otherwise have not found the relief for which they were looking. These patients may find PRP injections more acceptable and easier to tolerate than other interventions such as analgesics, steroid and non-steroid drugs, or physical therapy, allowing them to get the care and relief they desire. The use of HA is similarly acceptable but does have a different mechanism of action, therefore increasing the available choices.

CONCLUSION

The PRP procedure showed a higher degree of efficacy when compared to HA injections as well as significant findings of more and longer pain reduction, improved function, and patient satisfaction. This was particular noticeable in the treatment of younger patients with less severe articular cartilage degeneration. All of the studies suggest that PRP injections are a useful approach and alternative in the treatment of OA. This minimally invasive procedure appears to be safe and effective. It could be utilized as a reasonable treatment option should other therapies fail or are inappropriate for the particular patient.
However, the overall methodological quality of these three studies is considered to be low. More research is needed, with specific emphasis on blinded randomized control trials, to further confirm current positive findings and to determine the most effective platelet-concentration protocol, precise mechanism of action, its disease-modifying properties, possible long-term effects, and its cost effectiveness. A suggestion made by Spakova et al\textsuperscript{12} is intriguing, as they discussed possible studies on PRP and HA combination treatments to determine a possible synergistic effect and to potentially produce greater symptomatic relief for patients with OA. These studies also should have a larger sample size to increase reliability and attempt to decide upon a standard method of measurement to enhance comparison.
References


-22-
TABLE 1 Characteristics of Reviewed Studies, GRADE profile

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Study</th>
<th>Treatment (total)</th>
<th>Placebo or no treatment (total)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve Symptoms and Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 prospective cohort 1 retrospective cohort</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Kon et al11</td>
<td>150</td>
<td>100</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spakova et al12</td>
<td>120</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sanchez et al13</td>
<td>60</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 prospective cohort</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Kon et al11</td>
<td>150</td>
<td>100</td>
<td>Low</td>
<td>Important</td>
</tr>
</tbody>
</table>

*Sanchez et al does not provide post-treatment numbers to compare to outcome*

*Top three authors of Sanchez et al study showed conflict of interest as they worked for a company that commercially sells a system assisting with PRP preparations*
### TABLE 2 Outcome Scores for Kon et al\textsuperscript{11}

<table>
<thead>
<tr>
<th></th>
<th>PRP</th>
<th>LW HA</th>
<th>HW HA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IKDC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>41.2 ± 10.9</td>
<td>44.7 ± 6.6</td>
<td>47.3 ± 13.9</td>
</tr>
<tr>
<td>2 months</td>
<td>62.7 ± 14.0</td>
<td>61.7 ± 13.1</td>
<td>54.8 ± 15.6</td>
</tr>
<tr>
<td>6 months</td>
<td>64.0 ± 18.7</td>
<td>53.8 ± 13.7</td>
<td>54.0 ± 16.0</td>
</tr>
<tr>
<td><strong>EQ VAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>53.6 ± 18.3</td>
<td>51.2 ± 7.8</td>
<td>52.2 ± 12.5</td>
</tr>
<tr>
<td>2 months</td>
<td>73.0 ± 13.9</td>
<td>68.7 ± 13.5</td>
<td>63.0 ± 14.7</td>
</tr>
<tr>
<td>6 months</td>
<td>73.2 ± 17.3</td>
<td>61.7 ± 14.8</td>
<td>62.4 ± 15.2</td>
</tr>
</tbody>
</table>

IKDC = International knee document committee (Pain, function, ADL assessment); (0 = max. pain/Sx and loss of function, 100 = no pain/Sx and loss of function)

EQ VAS = Visual analogue scale for pain assessment; (0 = max. pain, 100 = no pain)

### TABLE 3 Outcome Scores for Spakova et al\textsuperscript{12}

<table>
<thead>
<tr>
<th></th>
<th>PRP</th>
<th>HA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WOMAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.76 ± 16.50</td>
<td>43.21 ± 13.70</td>
</tr>
<tr>
<td>3 months</td>
<td>14.35 ± 14.18</td>
<td>26.17 ± 17.47</td>
</tr>
<tr>
<td>6 months</td>
<td>18.85 ± 14.09</td>
<td>30.90 ± 16.57</td>
</tr>
<tr>
<td><strong>NRS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.27 ± 1.87</td>
<td>6.02 ± 1.77</td>
</tr>
<tr>
<td>3 months</td>
<td>2.06 ± 2.02</td>
<td>3.98 ± 2.27</td>
</tr>
<tr>
<td>6 months</td>
<td>2.69 ± 1.86</td>
<td>4.3 ± 2.07</td>
</tr>
</tbody>
</table>

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (Pain, function, ADL assessment); (0 = no pain/Sx and loss of function, 96 = max pain/Sx and loss of function)

NRS = 11-point pain intensity Numeric Rating Scale (Pain assessment); (0 = no pain, 10 = max pain)