

2015

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Recommended Citation

Gandhi, Darshit, "In the Treatment of Patients With Knee Joint Osteoarthritis, Are Platelet Rich Plasma Injections More Effective Than Hyaluronic Acid Injections?" (2015). *PCOM Physician Assistant Studies Student Scholarship*. 221.
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**In the treatment of patients with knee joint osteoarthritis, are
Platelet Rich Plasma injections more effective than Hyaluronic acid
injections?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

March 25, 2015

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "In the treatment of patients with knee joint osteoarthritis, are Platelet Rich Plasma injections more effective than Hyaluronic acid injections?"

Study Design: Review of one randomized double-blind trial, one randomized cohort study, and one randomized control trial published in the English language in the year 2012.

Data Sources: All studies were published in peer-reviewed journals found via the use of PubMed.

Outcome(s) Measured: Patients were divided into two groups: those who received platelet rich plasma injections (PRP) and those who received hyaluronic injections (HA). Efficacy of PRP injections was compared to the efficacy of HA injections. Outcomes were measured at baseline and various monthly intervals post treatment using WOMAC scores. In addition, outcomes were measured by giving the 11 point pain intensity Numeric Rating scale (NRS), IKDC, and KOOS scores.

Results: In two studies, results of PRP injections versus HA injections reached statistical significance and proved to be an effective form of treatment in patients with knee osteoarthritis ($p < 0.01$). In the third study, however, there was no statistical significance indicated in the use of PRP injections as compared to HA injections. More research studies are necessary to understand the full effect of PRP injections in the treatment of knee osteoarthritis.

Conclusion: Overall, PRP injections alone cannot be the first line of treatment used for knee osteoarthritis. However, PRP injections are a safe and viable option for patients who do not benefit from other treatments like HA injections. They also tend to have a better effect on patients with lower-grade knee osteoarthritis.

Key Words: Platelet Rich Plasma, Hyaluronic acid, Knee Osteoarthritis, Intra-Articular Injection

INTRODUCTION

Knee pain, joint aches, back pain and arthritis seem to be the staple signs of old age. It is also rather common among athletes, whose physical strain on the body makes it more prone to such wear-and-tear injuries. Osteoarthritis (OA) is a common type of condition that is associated with debilitating pain which leads to loss of function in mobility and decreases the patient's quality of life. Osteoarthritis, commonly known as wear and tear arthritis, is a condition in which a protective cartilage on the end of the bones wears down over time.¹ The most common locations on the body for osteoarthritis include, but is not limited to, the knees, hips, hands, neck, and lower back.¹ This paper focuses specifically on osteoarthritis of the knees.

The mechanism involved in OA develops as a result of failed attempts of the chondrocytes to repair the damaged cartilage. In addition, the increased water content causes the softening of the cartilage leading to fissuring and/or micro-fractures. It was also recently discovered that OA can result from the complex interaction of multiple factors such as joint integrity, cellular and biochemical processes, genetic predisposition, and local inflammation mechanical forces.² Some of the other risk factors associated with knee OA include age, obesity, trauma, occupational history, and genetic factors.

According to a study published in the *American Journal of Public Health*, osteoarthritis of the knees is one of five leading causes for disability among non-institutionalized adults.³ Knee and hip joint replacement procedures account for 35% of the total arthritis procedures conducted during a hospitalization.⁴ In 2006, OA was the principle diagnosis for 547,000 knee surgery hospitalizations in the United States.⁵ CDC data from 2005 shows that osteoarthritis affects 13.9% of adults aged 25 years and older and 33.6% (12.4 million) of those who are more than 65 years old in the United States.⁶ The incidence rate of symptomatic radiographic knee OA in

adults older than 20 years old is 240 per 100,000.⁷ Annually, the estimated cost of total knee replacement surgeries is \$28.5 billion.⁸ The total direct and indirect cost of OA was \$5700 per person in the fiscal year of 2000.⁹

The most common form of treatment for knee OA includes a combination of non-pharmacological approaches and various pharmacologic therapies, including oral, topical, intra-articular medications, and intra-articular injections such as hyaluronic acid (HA).² The final treatment option for knee OA is surgery. However, patients will often choose non-pharmacological and pharmacological treatments in order to delay the need for surgery. Autologous Platelet Rich Plasma (PRP) injection infuses growth factors into the patients' joint which prompts healing of the damaged knee joints. The use of Platelet Rich Plasma injections has also been shown to be effective in the treatment for reducing knee pain and improving function of knee joint in patients with knee OA in various non-randomized clinical studies. This paper evaluates one randomized double-blind trial, one randomized cohort study and one randomized control trial to compare the efficiency of Platelet Rich Plasma injections over Hyaluronic acid injection for the purpose of reducing knee pain and improving function of the knee joint in patients affected by Osteoarthritis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "In the treatment of patients with knee joint osteoarthritis, are Platelet Rich Plasma injections more effective than Hyaluronic acid injections?"

METHODS

For this review, a specific selection criteria was used to select one randomized double-blind trial, one randomized cohort study, one randomized control trial. All studies were selected

based on relevance and that the outcomes of the studies mattered to the patients (POEMs). All studies are published in English in peer-reviewed journals obtained via the use of PubMed. Keywords such as Platelet Rich Plasma, hyaluronic acid were used to generate these articles. Once the articles were generated, only randomized control trials published after 1999 were used for purpose of this review.

Although each of the trials had specific criteria, a common trend was seen in all three: patients exhibited chronic knee pain for at least 4 months and x-rays showed OA findings. The population used were individuals between the ages of 18 and 80. Any individuals with previous knee operation, autoimmune disease, anticoagulation therapy were excluded. The intervention used in each of the studies was platelet rich plasma injection and was compared to standard treatment of hyaluronic acid injection. The studies measured the reduction of knee pain and joint function in patients with OA when given PRP injections versus HA using various scales, including IKDC, KOOS and WOMAC scores. Table 1 exhibits the specific demographics and characteristics of the included studies, showing specifically the inclusion and exclusion criteria used for patients, their age and the interventions used in each study.

Table 1: Demographics & Characteristics of included studies

Study	Type	# of Patients	Avg Age (in yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cerza ¹⁰ (2012)	RCT	PRP: 60 HA: 60 Total: 120	PRP: 66.5 ±11.3 HA: 66.2 ± 10.6	Patients with clinically and radiographically documented grades I, II, or III gonarthrosis.	History of previous knee operations, previous infiltrative treatment of the affected knee, documented rheumatoid or autoimmune abnormalities and cases of grade IV gonarthrosis.	0	4 autologous PRP intra-articular injections (once a week for four weeks)
Filardo ¹¹ (2012)	Double-blind RCT	PRP: 54 HA: 55 Total: 109	PRP: 55 HA: 58	History of chronic pain or swelling of the knee for at least 4 months; presenting with OA on X-ray	Age ≥ 80 years; systemic disorders; anticoagulants therapy; use of NSAIDS in the 5 days before blood donation; Hb < 11 g/dl; PLT <150,000/mm ³ .	HA: 3	3 autologous PRP intra-articular injections (once a week for three weeks)
Spakova ¹² (2012)	Randomized Cohort Study	PRP: 60 HA: 60 Total: 120	PRP: 52.8 ± 12.43 HA: 53.2 ± 14.53	Chronic pain ≥12 months; and the radiologic signs of knee OA Grade 1, 2, and 3 according to Kellgren and Lawrence classification.	Hb < 10 g/dl; PLT <100,000/mm ³ ; systemic disease, hematologic disease, anticoagulant therapy, glucocorticoid injection or HA within 3 months	0	3 autologous PRP intra-articular injections (once a week for three weeks)

OUTCOMES MEASURED

The main outcome measured in all these studies is the effectiveness of Platelet Rich Plasma injections over Hyaluronic acid injections in treating patients with knee osteoarthritis. The secondary outcome measured in the studies was the effectiveness of PRP injections on various grades of knee osteoarthritis. Each of the studies compared patients who received platelet rich plasma injections with patients who received hyaluronic acid injections at weekly intervals. In the study by Spakova et al, data was measured at baseline, 3 and 6 months post-treatment

using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and the 11-point pain intensity Numeric Rating Scale (NRS). In the study by Filardo et al, data was evaluated before and at 2, 6, and 12 months after the treatment was administered by IKDC and KOOS scores. Finally, in the study by Cerza et al, the WOMAC score was measured before treatment and at 4, 12, and 24 weeks after the first injection. The specific statistical measures reported by the articles ranged from the use of p-values, one-way ANOVA scores to t-tests, and Tukey multiple comparisons test.

RESULTS

This review evaluates three randomized control trials to assess the efficacy of Platelet Rich Plasma injections over Hyaluronic Acid injection for the purpose of reducing knee pain in patients affected by osteoarthritis. In the study by Spakova et al, 63 men and 57 women with an average age of 53 years were enrolled in a prospective cohort study. Patients were randomly divided into two groups: one group of 60 patients were treated using intra-articular autologous PRP injections while the control group of 60 patients were treated using intra-articular HA injections. For both groups, injections were administered three times in weekly intervals. Data was measured at baseline, 3, and 6 months after the last treatment dose was administered. At the beginning of the study, there was no statistically significant differences between both groups in regards to their age, sex, average WOMAC score, and the 11-point pain intensity NRS.

At the conclusion of the study, it was determined that there was a statistical significance ($p < 0.01$). In the PRP group, there was an improvement in WOMAC score from the baseline at 38.76 ± 16.50 points to 14.35 ± 14.18 points at the 3-month follow up and to 18.85 ± 14.09 points at the 6-month follow up. Additionally, the NRS score improved from a baseline of 5.27 ± 1.87 points to 2.06 ± 2.02 points at 3-month follow up and 2.69 ± 1.86 points at the 6-month

follow up. In the HA group, the WOMAC score from the baseline of 43.21 ± 13.70 points improved to 26.17 ± 17.47 points at the 3-month follow up and to 30.90 ± 16.57 points at the 6-month follow up. Furthermore, the NRS score changed from a baseline of 6.02 ± 1.77 points to 3.98 ± 2.27 points at 3-month follow up and stayed at 3.98 ± 2.27 points at the 6-month follow up. In both cases, improvements were observed at the 3- and 6-month follow up with respect to the baseline levels.

Table 2: WOMAC and NRS Scores at baseline, 3-month and 6-month follow up

	Baseline		3-month Follow Up		6-month Follow Up	
	PRP	HA	PRP	HA	PRP	HA
WOMAC Scores	38.76 ± 16.50	43.21 ± 13.70	14.35 ± 14.18	26.17 ± 17.47	18.85 ± 14.09	30.90 ± 16.57
NRS	5.27 ± 1.87	6.02 ± 1.77	2.06 ± 2.02	3.98 ± 2.27	2.69 ± 1.86	3.98 ± 2.27

In the study by Filardo et al, out of 109 patients, 55 were treated with weekly HA injections and 54 were treated with weekly PRP injections. They were evaluated at 12 months of follow up. The patients in both groups received treatment once a week, for 3 weeks. In an attempt to keep the study double blinded, all evaluations were conducted by clinical staff members who were not part of the injective procedure and all patients underwent blood harvesting to obtain autologous PRP even though it was only used for half of them. Patients were evaluated at baseline and at their 2-, 6-, and 12-month follow ups. Data was collected using IKDC and KOOS scores after the treatment. In this study, 3 failures occurred, all in the HA group. Two of the patients who withdrew showed signs of intolerance to some component of HA and the third patient withdrew from the study due to complaints of intense pain and then pursued other treatment options.

At the conclusion of the study, it was determined that while both groups showed improvement from their baseline data, the comparison between the two groups was statistically not significant. In the PRP group, there was an improvement in IKDC score from the baseline at 50.2 ± 15.7 points to 62.8 ± 17.6 points at the 2-month follow up and to 64.3 ± 16.4 points at the 6-month follow up. In the HA group, the IKDC score from the baseline of 47.4 ± 15.7 points improved to 61.4 ± 16.2 points at the 2-month follow up and to 61.0 ± 18.2 points at the 6-month follow up. The KOOS scores showed a similarly trend. Detailed data is shown in Table 3 below.

Table 3: IKDC & KOOS Scores at baseline, 2-month, 6-month, and 12-month follow up

	Baseline		2-month Follow Up		6-month Follow Up		12-month Follow Up	
	PRP	HA	PRP	HA	PRP	HA	PRP	HA
IKDC Scores	50.2 ± 15.7	47.4 ± 15.7	62.8 ± 17.6	61.4 ± 16.2	64.3 ± 16.4	61.0 ± 18.2	64.9 ± 16.8	61.7 ± 19.0
KOOS	65.4 ± 17.7	63.1 ± 17.4	73.1 ± 21.5	71.1 ± 18.6	74.2 ± 19.6	73.2 ± 18.1	74.0 ± 19.4	74.0 ± 19.4

This study, however, did reveal two important findings. One, when comparing the two groups, a significantly higher post-injective pain reaction was observed in the PRP group ($p = 0.039$). This reaction was self-limiting and did not compromise the overall outcome. Also, this study observed that patients with low-grade articular degeneration had better results with the PRP injections at the 6 and 12 month follow-up even though it did not reach statistical significance ($p = 0.08$ and $p = 0.07$, respectively).

In the study by Cerza et al, 120 patients with clinically documented gonarthrosis were enrolled in this study. The patients were randomly divided into 2 groups of 60 patients. The PRP group received intra-articular injections of PRP while the HA group received intra-articular injections of HA. For both groups, injections were administered once a week for four weeks. The injections were administered by an unblinded physician. All patients were evaluated using a

WOMAC score at baseline, and at 4, 12, and 24 weeks after the treatment was initially administered.

At the conclusion of the study, it was determined that patients treated with the PRP injections showed statistically significant improvement in their WOMAC scores than compared to the patients in the HA group ($p < 0.001$). For the PRP group, the average WOMAC score at baseline of 76.9 ± 9.5 points improved to 49.6 ± 17.7 points at 4 weeks, 39.1 ± 17.8 points at 12 weeks, and 36.5 ± 17.9 points at 24 weeks. For the HA group, the average WOMAC score at baseline was 75.4 ± 10.7 points, 55.2 ± 12.3 points at 4 weeks, 57.0 ± 11.7 points at 12 weeks, and increased to 65.1 ± 10.6 points at 24 weeks. Additionally, it was revealed that patients with grade III gonarthrosis in the HA group showed a marked worsening ($p < 0.001$) while the grade III patients in the PRP group did not show any statistically significant differences.

Table 4: WOMAC Scores at baseline, 4 weeks, 12 weeks, and 24 weeks follow up

	Baseline		4-week Follow Up		12-week Follow Up		24-week Follow Up	
	PRP	HA	PRP	HA	PRP	HA	PRP	HA
WOMAC Scores	76.9 ± 9.5	75.4 ± 10.7	49.6 ± 17.7	55.2 ± 12.3	39.1 ± 17.8	57.0 ± 11.7	36.5 ± 17.9	65.1 ± 10.6

DISCUSSION

Presently, platelet rich plasma is used in maxillofacial surgery and increasingly accepted in the treatment of tendinopathy, acute and chronic muscular lesions, spinal fusion and other such orthopedic and sports medicine related injuries.¹⁰ This systematic review of three randomized control trials evaluated the efficiency of platelet rich plasma injections for patients with knee osteoarthritis. An advantage of using PRP injections as an effective form of treatment

is that it can be easily obtained with a simple centrifugation process. Since it is prepared from autologous blood, it eliminates concerns of allergic reactions or disease transfer in patients.

There were several notable limitations in the randomized control trials examined. First, each study used a different method to prepare the PRP injections. In the study by Spakova et al, a simple centrifugation process was used to minimize the cost of the injections. On the other hand, in the study by Filardo et al, a double-spinning high concentrate leukocyte PRP was used. The authors also froze the PRP injections to be used at a later time. The disadvantage of this process is that it could change the morphology and decrease the platelet function. This could potentially be a reason why this study did not reach statistical significance. Furthermore, the study by Cerza et al utilizes autologous conditioned plasma (ACP). Secondly, in two of the three studies reviewed, patient follow-up lasted approximately 6 months. A longer follow-up time frame could prove to be beneficial in understanding the full effects of the PRP injections on knee pain. Finally, the sample size for all the studies is too small. Including a greater population sample would allow the results to more accurately represent the effectiveness of PRP injections on a greater cross section of the patients who suffer from knee osteoarthritis.

The PRP injections proved to be more effective in patients with lower grade knee osteoarthritis (Grades I and II). The PRP injections also tend to have an initial increase in pain reaction in patients; however, this is a self-limiting issue and did not compromise the overall validity of any of the studies. Although more research is needed on the subject matter, the studies show that even if it is not more effective than HA injections, PRP injections are definitely a safe and viable option for treating patients with knee osteoarthritis who do not necessarily benefit from treatments like HA injections.

CONCLUSION

The answer to the proposed question is conflicting and inconclusive. The PRP injections seem to be more effective in the treatment of lower-grade osteoarthritis but more studies still need to be conducted to confirm this. Despite its wide application in clinical practice, there is little statistical findings reported of its efficiency in treating knee osteoarthritis over HA injections. Future studies should focus on how the different preparations of PRP injections would affect their effectiveness in treatment of knee osteoarthritis and in comparison to HA injections. For example, frozen double-spinning high concentrate leukocyte PRP was the only kind of PRP injection that did not reach statistical significance.¹¹ In another study, autologous conditioned plasma injections reached statistical significance. This type of PRP was chosen due to its high content of growth factors and a significantly decreased quantity of white blood cells.¹⁰ Research examining different concentrations of white blood cells in PRP injections could also prove to be beneficial in understanding the overall picture of how effective PRP injections can be in treating patients with knee osteoarthritis. Due to a lack of clinical findings, PRP injections should not be used as the first line of treatment for patients with knee osteoarthritis.

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