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Are Platelet-Rich Plasma Injections Effective at Reducing Pain in Adults With Knee Osteoarthritis?

Jessica Sebastian
Philadelphia College of Osteopathic Medicine

Are platelet-rich plasma injections effective at reducing pain in adults with knee osteoarthritis?

Jessica Sebastian, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "platelet-rich plasma injections are effective at reducing pain in adults with knee osteoarthritis?"

STUDY DESIGN: A systematic review of two double-blind, randomized controlled trials (RCTs) and one single-blind randomized controlled trial published after 2015. All studies were published in English.

DATA SOURCES: The two double-blind randomized controlled trials and one single-blind randomized controlled trial were found via PubMed. All sources were published in peer-reviewed journals and were chosen based on their relevance to the clinical question.

OUTCOMES MEASURED: Pain reduction was the outcome measured in all three studies using the WOMAC pain scale. In this systematic review, the level of pain was evaluated at baseline and 24 weeks (6 months).

RESULTS: In the double-blind RCT conducted by Cole et.al (*Am J Sports Med*. 2017;45(2):339-346. doi: 10.1177/0363546516665809), there was reduction in pain with platelet-rich plasma injections with a mean change from baseline of 2.89. However, no statistical significance was noted in this study. In the single-blind RCT by Lisi et al. (*Clin Rehabil*. 2018;32(3):330-339. doi: 10.1177/0269215517724193), reduction of pain was noted with a median change from baseline of 4, but no statistical effect was noted. Lastly, in the double-blind RCT by in Rahimzadeh et al. (*Clin Interv Aging*. 2018;13:73-79. doi:10.2147/CIA.S147757), there was reduction in pain with a mean change from baseline of 8.6, as well as statistical significance with a p-value of <0.001.

CONCLUSION: While clinical reduction was demonstrated by all three studies based on the decrease in mean change from baseline, statistical significance was not noted in the studies conducted by Cole et al. (*Am J Sports Med*. 2017;45(2):339-346. doi: 10.1177/0363546516665809) and Lisi et al. (*Clin Rehabil*. 2018;32(3):330-339. doi: 10.1177/0269215517724193). Thus, the results of this review are inconclusive. Future studies need to be designed in order to showcase statistical significance with the use of platelet-rich plasma injections in reducing pain in those with knee OA.

KEY WORDS: platelet-rich plasma injections, knee osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is one of the most common forms of arthritis in the knee and it occurs due to gradual breakdown of articular cartilage, leading to a decrease in defensive space between the bone. This results in bone contact, which can cause production of painful bone spurs in the affected area. Approximately 27 million Americans suffer from osteoarthritis, with prevalence continuing to increase with age. Individuals aged 25 and older have classified with a 13.9% rate of OA in at least one joint, with 33.6% of adults over 65 years suffering from OA as well.[1] In terms of cost, total costs for the treatment of OA in 2013 was approximately $16.5 billion dollars, making it the second most expensive health condition treated in U.S hospitals for that year.[2] Cost is even greater if the patient requires joint replacement surgery. In 2013 alone, OA accounted for 25.7 million healthcare visits and 3 million hospital stays, making it the primary cause of hospitalizations compared to other forms of arthritis.[3] In total, it represented 10% of all hospitalizations and 2% of ambulatory appointments.[3]

While the pathophysiology of knee OA is not fully understood, it encompasses a variety of factors, such as family history, age, obesity, inflammation mediators, joint space and trauma.[4] Symptoms of knee OA vary depending on the mechanism, but pain around the joint space is the most common manifestation which can fluctuate in intensity. This pain is most commonly noted in the morning and after prolonged sitting or rest. As OA is considered a major cause of pain and disability among adults in the US[3], physician assistants can play a large role in helping to properly diagnose and effectively treat these patients.

Treatment for OA varies from person to person and depends greatly on its severity and disruption to an individual's activities of daily living. The goal of treatment is to relieve patients of pain and improve their functionality, since there is no definitive way to prevent OA from

occurring. Some common nonpharmacological regimens for patients presenting with OA include exercise, heat and cold applications, weight loss, acupuncture, transcutaneous electrical nerve stimulation, and assistive devices.[5] Pharmacological treatment includes NSAIDs, duloxetine, capsaicin topical cream, opioid analgesics, and intra-articular injections.[5] A last resort for patients would be the surgical approach, which includes joint lavage, arthroscopic debridement, osteotomy, and joint replacement.[5]

The treatment options listed above all play a role in reducing symptoms in those with knee OA. However, long-term use of some therapies, such as prolonged NSAID and corticosteroid use, could result in other sequelae to the individual, such as putting them at risk for cardiovascular or gastrointestinal conditions. Since the only definitive cure for OA is surgery, often times individuals look for methods that can help alleviate symptoms associated with chronic OA. Platelet-rich plasma (PRP) injections may be used an alternative method that is minimally invasive and could help reduce pain in these patients. PRP injections are designed to help rebuild cartilage, repair torn ligaments, and reduce pain and swelling in hopes that certain patients are able to avoid surgery.[9] It is thought that by using one's own platelets, these injections could stimulate natural immune repair mechanisms and supply the growth factors necessary to build tissue.[9] This paper evaluates three randomized controlled trials (RCTs) evaluating the efficacy of platelet-rich plasma injections at reducing pain in adults with knee osteoarthritis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "platelet-rich plasma injections are effective at reducing pain in adults with knee osteoarthritis?"

METHODS

Three randomized controlled trials that investigated platelet-rich plasma injections as an intervention for pain reduction in adults with knee OA were chosen for this analysis. Authors Cole et al. and Lisi et al. compared platelet-rich plasma injections with intra-articular hyaluronic acid injections and Rahimzadeh et al. compared platelet-rich plasma injections with prolotherapy. All three studies looked at the efficacy of PRP injections in reducing pain in adults suffering with knee OA.

Articles were selected based on searches using the keywords “platelet-rich plasma injections” and “knee osteoarthritis”. The studies were published in peer reviewed articles and presented in the English language. They were searched via PubMed based on their relevance to the clinical question and if they included patient oriented outcomes. Inclusion criteria included studies that were published after 2015, randomized controlled trials, human species, and in English. Exclusion criteria included studies that were published in 2015 or earlier, studies with animals, or studies in a different language. The statistics reported and used in this systematic review were p-values, mean change from baseline, and standard deviation. Table 1 below demonstrates the demographics and characteristics showcased in the studies.

OUTCOMES MEASURED

The primary outcome measured in this selective EBM review was pain reduction in adults with knee OA at baseline and 24 weeks follow-up. All three articles used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale to assess pain. The WOMAC scale is a self-administered questionnaire that can assess an individual’s level of pain while completing daily activities, such as walking, climbing stairs, sleeping, resting, and

standing. The scores are totaled and calculated on the scale from 0-20, with 0 indicating no pain and 20 indicating extreme pain.[6-8]

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cole[6] (2017)	Double blind RCT	111	18-80 yrs old	Pts ages 18-80 yrs with Grade 1-4 radio-graphically diagnosed OA with unilateral sxs who are able to provide consent & have a mean VAS pain score >40 of 100 for >7 days in the previous month	Adults w/ knee instability, pregnancy, pretreatment VAS pain score <40, major axial deviation, anti-coagulation or NSAIDS use w/i 5 days of blood draw, bilateral symptomatic lesions, systemic ds, anemia, intra-articular injections or prior treatment w/ HA w/i 6 mo, history of known anemia	12	Platelet-rich plasma injection w/ a mean of 790 ± 0.11 WBCs/μL
Lisi[7] (2018)	Single blind RCT	58	>18 yrs old	Pt >18 with an MRI-proven Grade II/III knee OA w/o OA treatment, HA or steroid injection, active pregnancy, allergy to HA, or bacterial knee infection; has a life expectancy >1 yr, understands clinical scales, give consent	Not reported	8	Platelet-rich plasma injections with calcium gluconate as the activator
Rahimzadeh[8] (2018)	Double blind RCT	42	40-70 yrs old	Pts age 40-70 yrs & stage 1 or 2 OA	Adults w/ RA or hemophilia, prior knee surgery,	0	7mL platelet-rich plasma injections

					anti-coagulation or NSAIDs w/i 7 days, drug/alcohol addiction		

RESULTS

Cole et al. conducted a double-blind, randomized controlled trial comparing the effects of platelet rich plasma injections and hyaluronic acid (HA) intra-articular injections in adults with knee OA. A total of 111 patients specified for the treatment of knee OA were selected for this study and individuals were chosen based on specific inclusion/exclusion criteria as noted in Table 1 above.[6] The patients chosen were randomized with the use of an electronic randomization process into two groups – one group receiving intra-articular PRP and other group receiving intra-articular hyaluronic acid.[6] After treatment in both groups, patients were informed to limit the use of their leg for a minimum of 24 hours and to apply cold compresses as needed for discomfort.[6] They were recommended to partake in activities requiring only mild exertion, followed by a steady return to recreational activities as tolerated.[6] Three weekly injections were given to these patients and they were evaluated at baseline, treatment weeks 2 and 3, and follow-up weeks 6, 12, 24, and 52.[6] In order to keep consistency among all three studies, this EBM review will only focus on patient outcomes at baseline and 24 weeks follow-up. During the follow-up period, 11% of patients were lost to follow-up or were unwilling to complete the study, so the final study group consisted of 49 patients in the PRP group and 50 patients in the hyaluronic acid group.[6]

In this study, the WOMAC pain scale was used as a primary outcome measurement to evaluate the effectiveness of both interventions. The statistical data used to measure the outcomes before and after treatment were presented as mean values and standard deviation. The

level of significance was measured as a p-value <0.05 between both interventions.[6] As shown in Table 2 below, both interventions showed some improvement in pain when comparing values at baseline and 24 weeks follow-up.[6] The PRP group showed a decrease in mean values with 7.00 ± 0.53 before treatment and 4.11 ± 0.56 at 24 weeks, resulting in a mean change from baseline of 2.89.[6] The HA group demonstrated a decrease in mean values of 7.52 ± 0.58 before treatment and 5.00 ± 0.50 after treatment, with a mean change from baseline value of 2.52.[6] Although trends towards improvement of pain is seen slightly greater in the PRP group, there is no statistical significance when comparing both interventions (p = 0.93), implicating a small treatment effect.[6] Furthermore, this study did not discuss compliance, tolerability, or adverse effects among patients in this trial.

Table 2. WOMAC Mean ± SD Change in Pain from Baseline and 24 Weeks Follow-Up and Statistical Significance (data from Cole et al.[6])

	Before Treatment (Mean ± SD)	**24 weeks (Mean ± SD)**	**Mean Change from Baseline (calculated)**	**P-value**
PRP Group	7.00 ± 0.5	4.11 ± 0.56	2.89	0.53
HA Group	7.52 ± 0.58	5.00 ± 0.50	2.52	

Lisi et al. is a single-blind randomized controlled trial comparing the efficacy of platelet-rich plasma injections and hyaluronic acid injections in patients with knee OA. Fifty-eight patients were chosen for this study based on the eligibility criteria listed in Table 1.[7] Patients were randomized into either group and if they demonstrated bilateral knee OA, both knees were treated with the treatment that was assigned to them.[7] The groups were given their allocated treatments at an outpatient office from the same study staff at four weeks intervals, using a superolateral advancement into the suprapatellar pouch. [7] Patients were monitored for 10-15 min after the injections to check for adverse reactions and then discharged home with no restrictions, as well as being instructed to take pain medications as needed.[7] A total of eight patients were

excluded from the final analysis due to unspecified reasons, so the final study group for analysis consisted of 28 patients for the PRP group and 22 patients in the HA group.[7]

The WOMAC pain scale was one of the measurements utilized to detect the effectiveness of both interventions in reducing pain in these patients. Data were analyzed at baseline, 15 days, 6 months, and 12 months.[7] In order to maintain consistency among the studies in this review, data collected at baseline and 6 months will be further discussed. Median values were analyzed at these intervals, with the level of significance measured as a p-value <0.05.[7] According to Table 3 below, both treatment groups showed some degree of improvement in pain when compared to the baseline values.[7] The PRP group showed a decrease in median values with 4 before treatment and 0 at 6 months, resulting in a median change from baseline of 4.[7] The HA group demonstrated a decrease in median values of 7 before treatment and 3 after treatment, with a median change from baseline value of 4 as well.[7] When comparing both intervention groups, there was no statistical significance ($p = 0.91$).[7] Researchers of this study stated that there were no adverse effects observed in the intervention group or the control group.[7] Compliance and tolerability were not discussed in this study.

Table 3. WOMAC Median Change in Pain from Baseline and 6 Month Follow-Up and Statistical Significance (data from Lisi et al.[7])

	Before Treatment (Median)	**6 Months (Median)**	**Median Change from Baseline (calculated)**	**P-value**
PRP Group	4	0	4	0.91
HA Group	7	3	4	

Rahimzadeh et al. is a double-blind randomized controlled trial comparing the effects of platelet-rich plasma injections against prolotherapy (PRL) in those with knee OA. A total of 42 patients were chosen for this study based on the inclusion/exclusion criteria listed in Table 1.[8] Block randomization was used to assign the patients to either the intervention group or the control group.[8] Following proper monitoring of patients' vital signs, samples were produced and

7mL of separated plasma was given to patients in the PRP group while 7mL of 25% dextrose was given to those in the PRL group.[8] Following the administration of both treatments, patients were monitored briefly and discharged home if no adverse effects were noted.[8] There was no comment regarding losses to follow-up noted in this study.

The WOMAC pain scale was used to monitor the level of pain in these patients and data was collected at baseline, 1 month, 2 months, and 6 months later.[8] This review analyzed patients' pain levels at baseline and 6 months using the statistical data of mean values and standard deviation. Repeated-measures ANOVA was used to calculate the p-values for each specific intervention, with the level of significance being measured at $p < 0.05$.[8] According to Table 4 below, both the PRP group and the PRL group showed improvement in pain levels from baseline. The PRP group showed a decrease in mean values of 14.8 ± 1.5 at baseline and 6.2 ± 2.1 at 6 months, which resulted in a mean change from baseline value of 8.6.[8] The PRL group demonstrated a decrease in values of 14.6 ± 1.4 at baseline and 8 ± 1.6 at 6 months, resulting in a mean change of 6.6.[8] Each intervention individually showed statistical significance in reduction of pain ($p = <0.001$).[8] While it was mentioned that no adverse effects were noted from either intervention group, information regarding compliance and tolerance was not discussed.[8]

Table 4. WOMAC Mean ± SD Change in Pain from Baseline and 6 Month Follow-Up and Statistical Significance (data from Rahimzadeh et al.[8])

	Before Treatment (Mean ± SD)	**6 Months (Mean ± SD)**	**Mean Change from Baseline (calculated)**	**P-value**
PRP Group	14.8 ± 1.5	6.2 ± 2.1	8.6	<0.001
PRL Group	14.6 ± 1.4	8 ± 1.6	6.6	<0.001

DISCUSSION

Osteoarthritis can be a chronic, debilitating condition for many individuals suffering with it on a daily basis. OA in the knee specifically is responsible for major wear-and-tear of the knee joint and the surrounding capsule, making it a substantial burden in activities of daily living.[3] This systematic review looked into the efficacy of platelet-rich plasma injections as an intervention to assist with pain reduction in these specific individuals. All three studies evaluated a mean change of pain from baseline to 24 weeks follow-up. Cole et al. and Lisi et al. both demonstrated some improvement in pain with a mean change from baseline of 2.89 and 4, respectively.[6,7] However, statistical significance of this specific treatment was not mentioned in either study, making it difficult to determine the pure efficacy of PRP injections in reducing pain. On the other hand, Rahimzadeh et al. did demonstrate statistical significance in the improvement of pain with PRP with a mean change from baseline of 8.6 and p-value <0.001.[8] While all three studies did reveal clinical improvement in pain with this intervention, it is unclear whether or not it is statistically effective in the reduction of pain in those with knee OA.

There were various limitations noted among the studies used in this review. In Cole et al., authors mention that there was a difference in BMI between the two intervention groups, which could have contributed to some discrepancies in data.[6] Another limitation was a lack of a sham control group in this study, which would have been an appropriate addition in order to further evaluate the efficacy of these interventions.[6] In Lisi et al., some limitations mentioned were small sample size, limited number of injections given, and short follow-up intervals.[7] Authors stated that in order to accurately measure patient outcomes, further studies should look towards making standardized thresholds in terms of number of injections, intervals between injections, and local anesthesia.[7] Lastly, in Rahimzadeh et al., limitations included lack of a control group

receiving placebo, absence of proper evaluation of cartilage and soft tissue surrounding the knee joint, and short time allotted for proper patient assessment.[8]

The use of platelet-rich plasma injections was first noted to be valuable in an open-heart surgery in 1987 and has since then expanded into in various healthcare settings, such as to assist in healing after spinal injuries and help with sports-related injuries.[9] There are multiple variations of PRP preparations that are commercially available to use in the US.[9] Since PRP injections are prepared from autologous blood from the patient themselves, there are minimal risks noted in terms of disease transmission and immunogenic reactions in those receiving this treatment.[9] However, with any sort of injection, adverse effects such as infection at the site or scar tissue formation may be seen in patients. One issue that can arise with the use of these injections is that most insurance plans do not provide coverage for cost, so patients pay out-of-pocket with prices ranging from $200-$500.[9] These factors need to be taken into consideration in deciding whether or not PRP injection therapy is the best option for patients suffering with knee OA.

CONCLUSION

Based on the scope of this systematic review, while there was a clinical reduction in pain according to the decrease in mean change from baseline with the WOMAC pain scale, statistical significance of the specific treatment group was not reported in two of three studies. Thus, the results of this review are inconclusive. Further studies should be performed to provide statistical analysis of this intervention in regard to its efficacy in pain reduction from baseline. These future studies can also aid in determining if platelet-rich plasma injections vary in efficacy compared to other conventional treatment options available. Along with increasing sample size and follow-up intervals, future studies should take into consideration the level of physical exercise before and during follow-up intervals, as this can have an effect on the patient's outcome. It is also

important to closely monitor safety, tolerability, and adverse effects of platelet-rich plasma injections long-term. Knee osteoarthritis is a chronic condition that will continue to affect the daily functioning of individuals, so thorough randomized controlled trials need to be proposed in order to accurately see the possible benefits of platelet-rich plasma injections in reducing pain in these patients.

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