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Are PRP Injections Effective at Decreasing Chronic Low Back Pain in Adults?

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ABSTRACT

OBJECTIVE: The objective of this selective evidence based medicine review is to determine whether or not "Are PRP injections effective at decreasing chronic low back pain in adults?"

STUDY DESIGN: Systematic review of two randomized control trials and one prospective clinical evaluation written in English, published after the year 2012.

DATA SOURCES: All three articles were found in peer review journals published via PubMed Database.

OUTCOME MEASURED: The primary outcome measured in each study is self-reported pain at baseline and 4 weeks following injection of PRP or the comparison. The visual analog scale and a generic numeric rating scale were used to measure pain.

RESULTS*:* 1 of the 3 studies found PRP injections to be statistically effective at decreasing low back pain in adults at the time period assessed. Wu et al found that, at 4 weeks post injection, pain scores on a scale of 0 to 10 were on average 3.84 points less when compared to baseline scores ($p<0.05$) and were significantly lower at all other time points as well (*Pain physician*. 2016;19(8):617. https://www.ncbi.nlm.nih.gov/pubmed/27906940). Singla et al found no significant difference in pain levels at 4 weeks post injection when compared to the steroid control group but found a 75% reduction in VAS at 4 weeks when compared to baseline scores (*Pain practice: the official journal of World Institute of Pain*. 2017;17(6):782-791. https://www.ncbi.nlm.nih.gov/pubmed/27677100. doi: 10.1111/papr. 12526). The Tuakli-Wosornu et al study also revealed no significant difference in pain at 4 weeks when compared to baseline ($p=0.215$), but participants did have significant improvement regarding pain, function, and patient satisfaction over 8 weeks (*PM R*. 2016;8(1):1-10. https://ezproxy.pcom.edu/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=jlh&AN=112177067&site=eds-live&scope=site. doi: 10.1016/ j.pmrj.2015.08.010).

CONCLUSIONS: This review finds conflicting evidence that PRP injections are more effective than other treatment for chronic low back pain. The 2 RCTs did not show significant decrease in pain at the 4 week follow up time assessed, and the remaining study had severe limitations. Regardless, all three studies did show statistically significant improvement by the end of each study, so this review finds stronger evidence to support PRP injections for adjunctive use in adults with chronic low back pain.

KEY WORDS: Lumbar OR lower back, PRP OR platelet-rich plasma

INTRODUCTION

An estimated 84% of adults have low back pain at some point in their lives.[1] Most cases are self-limiting and resolve within 6 weeks.[1] Chronic low back pain is defined as pain persisting longer than 12 weeks.[2] The cause is often multifactorial and difficult to diagnose. Intervertebral discs are the origin of 40% of reported back pain and are the largest avascular structure in the human body, contributing to the disc's inability to regenerate and heal.[3] Facet joints are synovial joints of the spine that, with overuse and injury, can degenerate and cause a release of inflammatory mediators, capsular stretch, entrapment of synovial villi between articular surfaces, and nerve impingement by osteophytes.[4] Nearly 15-52% of patients have low back pain caused by lumbar facet joint syndrome.[4] The sacroiliac joint has been found to be the primary point of pain in 10% to 27% of adults with chronic low back pain, usually owing to injury.[5] Back injuries are more common in patients younger than 45, and disc disorders increase in frequency as the population ages.[6]

Secondary only to skin disorders, low back pain is one of the most common reasons people visit their primary care provider. In 2013 there were an estimated 62 million visits to hospitals, emergency departments, outpatient clinics, and physician offices,[6] and costs estimated at $87.6 billion make low back pain the third largest condition of health care spending.[7] These statistics do not include visits to chiropractors and physical therapists.

For patients with chronic low back pain, management can be a lengthy and trial-by-error process. Initially, patients are encouraged to utilize nontherapeutic treatments such as stretching, exercise, and heat application, as well as psychological therapies such as CBT and biofeedback.[1] Adjunctive therapies for short-term management of symptoms include spinal manipulation, acupuncture, or massage.[1] For more severe pain symptoms, pharmacologic therapy is used along

with nonpharmacologic measures.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are first line, and if contraindicated acetaminophen is recommended.[1] If these are ineffective, duloxetine, tramadol, cyclobenzaprine, and epidural injections may be utilized.[1] Neuropathic pain can be treated with alpha-2-delta ligands such as gabapentin.[7] Surgery, although unlikely to cure low back pain, can improve pain levels. Surgical indications include cauda equina syndrome, cancer, infection, severe spinal deformity, or persistent morbidity despite treatment with conservative measures for 6 months.[7]

Although the above treatments have some proven efficacy when compared to placebo in clinical trials, chronic low back pain continues to decrease the quality of life for millions of Americans. Platelet rich plasma (PRP) has been shown to be effective in treating many different musculoskeletal disorders and may be used as combination therapy with the above treatments, leading to improvement in quality of life. PRP consists of a high concentration of platelets derived from the patient's own peripheral venous blood. PRP is composed of bioactive proteins that influence the healing of tendons, ligaments, muscles, and bones; as well as growth factors and cytokines including platelet-derived growth factor, transforming growth factor-B, fibroblast growth factor, insulin-like growth factor 1, connective tissue growth factor, and epidermal growth factor.[4] These components work to promote cell proliferation, matrix regeneration, and angiogenesis. Growth factors and cytokines injected at a high concentration directly at the site of collagen injury or degeneration can act as humoral mediators to induce the natural healing cascade. In addition, they produce an anti-inflammatory effect and lab studies indicate that PRP possesses antimicrobial properties that contribute to a decreased risk of infection.[5] PRP has been shown in previous studies to be effective at reducing pain and

functional disability in conditions such as tennis elbow, knee osteoarthritis, achilles tendinopathy, and chronic patellar tendinosis.[5]

Physician assistants are likely to encounter patients with chronic low back pain regardless of their chosen specialty. Given the method of administration, affordability, and accessibility, PRP is a treatment option deserving closer consideration.

OBJECTIVE

The objective of this selective evidence based medicine review is to determine whether or not "Are PRP injections effective at decreasing chronic low back pain in adults?"

METHODS

This review evaluates three peer-reviewed articles that assess the efficacy of PRP in reducing chronic low back pain. Two studies used control injections for comparison: contrast[3] and methylprednisolone with lidocaine and saline.[5] The three studies include a prospective clinical trial; a prospective, double blind randomized control study; and a prospective randomized open blinded end point study that have not been previously used in a systematic review or meta-analysis. Participants were 18 years of age or older with diagnosed chronic low back pain. See Table 1 for specific inclusion and exclusion criteria for each individual study. Pain intensity was assessed before and after administration of PRP or the control agent at different time intervals. Each article reported pain evaluated at different intervals and reported pain accordingly. This paper will focus on the pain reports collected prior to intervention and 4 weeks post-injection. The statistics used to evaluate pain intensity are mean pain scores with standard deviation, paired t-test, and p-values.

Key words used to search for the studies were "low back OR lumbar", and "PRP OR platelet rich plasma". Each article was published in English and found via PubMed database with

the inclusion criteria of publication after the year 2012 and randomized controlled trials. Only two randomized controlled trials were identified that matched these criteria, so the prospective clinic evaluation was selected based on its relevance to the objective. All three articles were selected based on patient oriented outcomes. Exclusion criteria included patients under the age of 18 and those with acute low back pain.

TABLE 1: Demographics & Characteristics of Included Studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Singla[1] (2017)	RCT	40	18-65	Patients >18 with chronic low back pain of moderate intensity for >3 months; unilateral SIJ pathology on XR, MRI or nuclear scan with 3 or more + provocative tests.	Systemic or localized infection; spinal path that might impede recovery; history of intervertebral disk disease; pregnancy; active radicular pain; immunosuppressive conditions; allergy to medications used; narcotic use, CI pertaining to the use of platelet concentrate.	0	3mL of PRP with 0.5mL of calcium chloride into ultrasound guided SIJ injection
Tuakli-Wosornu[2] (2016)	RCT	47	>18 yrs	Refractory low back pain for >6 months; failure of conservative treatment; maintained intervertebral disk height of at least 50%; disk protrusion <5mm on MRI or CT; concordant pain on diskography; presence of a grade 3 or 4 annular fissure; absent CI	Presence of known bleeding disorder; current anticoagulation therapy; pregnancy; systemic or local infection; allergy to contrast agent; psychiatric condition; solid bone fusion preventing access; severe spinal canal compromise; extrusions or sequestered disk fragments; previous spinal surgery; spondylolysis; spondylolisthesis; discordant pain on diskography; presence of grade 5 annular fissure	4	1-2mL injection of autologous PRP into symptomatic degenerative intervertebral disks.

Wu[3] (2016)	Prospective clinical evaluation	19	38-62	Continuous or intermittent low back pain; local or paraspinal pain with or without radiation, increase of pain on flexion, rotation, or lateral bending, absence of neuro deficit, XR showing findings of lumbar facet joint degenerative changes	Radicular neuro complaints or with evident disc herniations, prior surgery on the spine, intolerance of local anesthesia and contrast media	0	Injection under fluoroscopy of 1-2mL of autologous PRP after injection of 0.5% lidocaine and nonionic contrast was administered locally.

OUTCOMES MEASURED

The outcome measured in all three studies was the self-reported pain score of patients 4 weeks after PRP injection, evaluated using the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS). Both require the patient to rate their pain based on a 0 to 10 scale, with 0 being no pain and 10 being the worst pain imaginable.

RESULTS

The prospective clinical evaluation by Wu et al included 8 men and 11 women with diagnosed lumbar facet joint pain who failed other interventions for at least 3 months prior to the study.[4] Exclusion criteria included evident disc herniations and prior surgery, because these were identified as independent variables that affect pain relief after intra-articular facet joint injections.[4] A CBC was performed on the patient's peripheral blood before treatment and on the centrifuged PRP to ensure the platelet concentration in the PRP was about 4 to 5 times greater than that in the native peripheral blood. Patients were injected with approximately 1-2 mL of autologous PRP under fluoroscopy by a spine surgeon. There was no control injection group. No complications were observed throughout the procedures.[4] Participants were instructed to rest and not to bend at the waist for one week. The results state that patients were given pain relief information and that "there was no anti-inflammatory treatment for patients during the 3 month follow-up period", suggesting that patients could not take NSAIDs at home.[4] The VAS was

conducted immediately following treatment and at 1 week, 1 month, 2 months, and 3 months post-procedure. The mean VAS scores for low back pain at rest were 7.05 before treatment and 3.21 at 4 weeks (Table 2).[4] A p-value of < 0.05 was calculated using the SPSS version 19.0 program.[4]

Table 2: Mean VAS Pain Scores at baseline and 4 weeks in Wu et al

	Baseline	4 weeks post-op
Mean	7.05	3.21
P-value	<0.05	

Singla et al conducted a prospective randomized open blinded end point study that included 40 patients with chronic low back pain who were previously diagnosed with sacroiliac joint (SIJ) pathology.[5] Patients had unilateral SIJ pathology on imaging with baseline VAS scores of greater than 3 for at least 3 months.[5] Patients on greater than 60 mg of morphine equivalent doses of opioids were excluded due to their altered pain responses. The participants were allocated into 2 groups randomly by computer-generated numbers and the sequence was placed into sealed, opaque envelopes. Both the patients and investigators were blinded to the injectant given at the time of the procedure. There were no significant differences in the baseline parameters between the two groups. Under guidance of ultrasound, the comparison group (Group S) received 1.5 mL of methylprednisolone with 1.5 mL of 2% lidocaine and 0.5 mL of saline while the treatment group (Group P) received 3 mL of PRP with 0.5 mL of calcium chloride.[5] There were no major complications.[5] The mean platelet content in the PRP was 2.94 ± 1.43.[5] All pain medication including NSAIDs were discontinued for the duration of the study, but those with diagnosed ankylosing spondylitis continued Sulfasalazine therapy. Patients were followed up at 2 weeks, 4 weeks, 6 weeks, and 3 months for assessment of pain intensity using the VAS. The percent change in score from baseline calculation formula was provided. Data was compared between the 2 groups using the Mann-Whitney U-test, and the follow up VAS scores were

compared to baseline with post hoc analysis using Bonferroni correction.[5] All patients were analyzed in the groups to which they were randomized, and none were lost to follow up. The median VAS scores for Group P were 7.5 and 1.5 at pre-injection and 4 weeks, respectively.[5] The median VAS score for Group S went from 6 pre-injection down to 3 at 4 weeks.[5] According to the calculated p-values, there was no statistically significant difference between groups at either time period. At 4 weeks, 75% of patients in Group P and 70% of patients in Group S had a reduction in VAS $\geq$ 50%, with a p-value of 0.723.[5] Therefore, there was no significant difference in patients having $\geq$ 50% reduction in VAS score at 4 weeks among the two groups.[5]

Table 3: Median VAS Pain Scores at baseline and 4 weeks in Singla et al

	PRP Group (n=20)	Steroid Group (n=20)	P-value
Median (Interquartile Range) at baseline	7.5 (5-8)	6 (5-7)	0.132
Median (Interquartile Range) at 4 weeks	1.5 (1-3)	3 (2-4)	0.054
Reduction in VAS at 4 weeks	75% (15)	70% (14)	0.723

The randomized controlled study performed by Tuakli-Wosornu et al included 47 participants with chronic axial low back pain, diagnosed via discography.[3] A total of 109 participants were assessed for eligibility from 2009 to 2013 at an academic outpatient spine practice. Fifty-eight were chosen and randomized for inclusion into the study. After discography, 7 were disqualified based on exclusion criteria, 3 failed to maintain inclusion and exclusion criteria throughout, and 1 was lost to follow up.[3] Notable exclusion criteria include disk protrusion >5 mm because targeted annular therapy would likely be to no avail, and grade V annular fissures because the injectate would likely flow out of the disk into the epidural space, lessening the opportunity for the PRP to have an effect.[3]

About 2 weeks prior to treatment baseline blood samples were taken to assess blood counts, ESR, and PT/INR to ensure they were within normal limits. Randomization was performed by an independent observer who drew cards from a sealed envelope to form a treatment and control group with a 2:1 ratio, respectively. There was a significantly greater number of females randomized to the control group than the treatment group, but other demographics were not significantly different.[3] During injection of 1-2 mL of either PRP or a contrast agent, the syringe was covered with an opaque sleeve to ensure that contents were not visible to the physician or the patient. There were no reported complications.[3] All participants were followed with questionnaires at designated time points for one year, and a subset was followed for up to 2 years. If a participant did not meet a minimal clinically significant outcome, they were unblinded at 8 weeks and offered intradiscal PRP if they were part of the control group. The NRS is commonly presented as a 100 mm horizontal line on which pain intensity is labeled from 0 to 10. Differences in mean PRP group scores at follow up time points compared with those at baseline were assessed using paired t-tests. Measures of the association between groups were calculated using odds ratios with observed level of significance determined by Pearson X^2 test. Mean NRS score at baseline was 4.61 and 4.74 for the control and PRP groups, respectively.[3] At 4 weeks, mean NRS score was still 4.61 for the control group and dropped to 4.0 for the PRP group.[3] The p-value of 0.157, however, reveals an insignificant change between the two groups.

Table 4: Median VAS Pain Scores at baseline and 4 weeks in Tuakli-Wosorni et al

	PRP Group (n=29)	Control Group (n=18)
Mean $\pm$ SD at baseline	4.74 $\pm$ 2.21	4.61 $\pm$ 2.21
Mean $\pm$ SD at 4 weeks	4.00 $\pm$ 2.21	4.61 $\pm$ 2.21
P-value	0.215	0.157

The safety of sterile PRP injections was revealed throughout all three studies based on the lack of serious complications. Singla et al found that pain and stiffness post injection was higher in Group P when compared with Group S, but the symptoms were transient, local, and mild in nature.[5] These symptoms are thought to be due to the stimulation of the body's natural response to inflammatory mediators rather than the injection technique.[5]

Table 5: Adverse Events Reported in PRP Groups

Study	PRP Group Size	Adverse Event
Singla et al [4]	20	Post injection pain and stiffness (n=9) Chest pain and difficulty breathing (n=1) Contralateral pain (n=1)

DISCUSSION

Wu et al found that participants had an average decrease of almost 4 points in their pain score rating 4 weeks after PRP injection.[4] Pain scores improved even further by the end of the 3 month follow up period, supporting the effectiveness of PRP for chronic low back pain. However, lack of comparison with a control group weakens the validity of this study.

In the Singla et al study Group S had a significant increase in pain scores at 3 months as compared to 2 and 4 weeks, lending to the short-term action of steroids.[5] This demonstrates that anti-inflammatory changes alone are not enough to reduce pain and disability long-term in patients with SIJ pain. The addition of growth factors enhances the biologic environment and improves tissue homeostasis. Although the findings were not significant at 4 weeks, the difference in VAS scores was significantly lower in Group P than Group S at 6 weeks and 3 months.[5]

Results of the Tuakli-Wosornu et al study revealed no statistically significant improvement in current pain at 4 weeks post injection when compared with controls.[4] However, over the 8 weeks of follow up there were significant improvements in other measured outcomes:

best pain, function, and patient satisfaction. Furthermore, those who received PRP reported an improvement in function through at least one year of follow up.[4]

Disadvantages of PRP include the variance of composition from subject to subject and possibly a small amount of growth factors.[3] Two of the three studies performed cell content analysis on the PRP samples, ensuring uniformity and controlling for differences in quality of the treatment.[4,5] All 3 studies had limitations in common including a relatively low number of participants, making it difficult to apply the results to the general population. None of the studies reviewed post procedure imaging to assess the effect that PRP had on the individual disease processes. Doing so would allow for determination of the best candidates for this procedure.

The Wu et al study had many limitations due to the small sample size, lack of a control group, minimal follow up time of just 3 months, and lack of follow up imaging.[4] There was a complete lack of information about allowed use of other pain relievers. No labs were completed and only subjective evidence was taken into consideration.

Singla et al had an important strength unique to all the studies: they controlled the use of all other pain medication, including NSAIDs, throughout the study.[5] Additionally, PRP was injected under ultrasound guidance, improving accuracy and limiting radiation exposure. Limitations of this study included a wide variability in the platelet count of PRP, short follow up time, and they allowed the continued use of sulfasalazine in participants who were diagnosed with ankylosing sponydlitis.[5]

The double-blind, randomized, controlled trial design, lengthy and rigorous selection process for participants, and long-term data were among the strengths of the Tuakli-Wosornu et al study.[3] A limitation was the short follow up time of only 8 weeks for the control group. There was no data collection on the cell counts or biochemical analysis of the PRP used in this study.

CONCLUSION

Steroids and other current treatment recommendations have been shown to offer short term relief of low back pain, but there is still a need to investigate long-lasting treatments that address the disease process itself. This review evaluated relief of low back pain 4 weeks after PRP injection and found that 2 of the 3 studies showed no statistically significant improvement vs the control group,[3,5] and the third has substantial limitations discrediting validity.[4] However, each study demonstrated improvement of pain after PRP injection in comparison with the baseline pain rating, and although this is not statistically significant it could still be clinically significant. This leads to the conclusion that PRP injections are effective at decreasing chronic low back pain in adults. PRP resolves the concern of long-term adverse effects of continuous intra-articular steroid injection and appears to have longer lasting benefits.[5]

Future studies should combine the strengths of the studies evaluated in this review. The use of adjunctive pain medication should be restricted to offer better control. The studies should be designed with a longer follow-up time frame so that differences between groups over time can be detected, as well as the duration of action of PRP on different disease processes and patient populations. This would allow for determination of treatment schedules. It is currently unclear whether multiple injections improve or worsen outcomes. Follow up should include routine radiologic studies to objectively guide this process and determine the extent of anatomical improvement of degeneration and injury as compared with baseline imaging. Administration of studies meeting these criteria can demonstrate PRP injections to be an affordable, safe alternative to current treatment options, in addition to improving the disability status of adults with chronic low back pain.

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