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Research Article

Treatment of Unresolved Shoulder Pain with Platelet-Rich Plasma Therapy

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Abstract

Background : Platelet-rich plasma (PRP) is a minimally invasive surgical alternative that uses platelets from a patient's own blood to heal musculoskeletal conditions. The objective of this study was to report the outcomes of patients with unresolved shoulder pain in response to PRP injections.

Methods : 52 patients and 61 shoulders underwent a series of one through seven PRP injections for unresolved shoulder pain. Patients were separated into three groups based on number of PRP treatments received. Group 1 received 1 treatment, Group 2 received 2 treatments and Group 3 received 3 or more treatments. Patients in Group 2 received a series of treatments 20.22 days apart and patients in Group 3 received treatments 20.00 days apart. Outcomes of resting pain, active pain, upper functionality scale and overall improvement percentage were compared to baseline and between groups. Group 1 reported outcomes a mean 4.79 months after treatment, Group 2 reported outcomes a mean 6.97 months after treatment, and Group 3 reported outcomes a mean 7.38 months after treatment.

Results : Patients who received one treatment experienced significant improvements in active pain and functionality when compared to baseline and also experienced 38.35% total overall improvement. Patients in Groups 2 and 3 experienced significant improvements in resting pain, active pain, and functionality score in addition to experiencing 48.33% and 55.53% total overall improvement respectively.

Conclusions : These results are encouraging and provide evidence that PRP may be an effective treatment modality for unresolved shoulder pain and warrants further investigation.

Keywords: Platelet-Rich Plasma; Shoulder Pain; Regenerative Medicine; Surgical Alternative

Introduction

Shoulder pain is the third most prevalent musculoskeletal pain, with a lifetime prevalence of up to 70% [1,2]. This debilitating condition causes pain, reduced range of motion, and decreased quality of life among millions of Americans each year [1,3]. The three most common causes of shoulder pain are acute injury, localized arthritis and genetic influences [4]. The pain is primarily focused within the rotator cuff, glenohumeral joint, acromioclavicular joint and referred neck pain [3,5]. Depending on the severity of the shoulder pain, recovery rates can be slow and are easily susceptible to recurrence at the site of the injury [6].

The diagnosis of shoulder pain may be troublesome within itself. Prognostic testing is not always advised due to lack of evidence and validity, especially with Magnetic Resonance Imaging (MRI) [5]. Studies have found common error with MRI by diagnosis of several shoulder pathologies without accompanied symptomatic pain [7-10]. These diagnoses may cause a recommendation for surgeries, which are associated with adverse effects. For example, a recent systematic review found that 79% of patients re-tear their rotator cuff after surgical repair [11] and 11.6% of patients who underwent shoulder arthroplasty experienced adverse complications [12]. These surgical risks demonstrates the need for a reliable, conservative approach for treating chronic shoulder pain.

A potential treatment modality to fill this void is Platelet-Rich Plasma (PRP) therapy. PRP is a concentrate derived from whole blood through centrifugation for the retrieval of platelets in a small volume of plasma. These components contain growth factors that promote tissue healing and regeneration [13-15]. PRP also generates an anti-inflammatory response, which is beneficial, as inflammation causes delayed wound healing and tissue growth [16,17]. Tissue regeneration and suppressed inflammation may work in a synergistic manner to effectively alleviate pain.

A consensus paper on the use of PRP in sports medicine commissioned by the International Olympic Committee

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supports the idea that PRP-derived growth factors can not only help restore shoulder function but also assist clinicians in meeting the high repair standards and tolerances that athletes expect in cartilage, ligament, meniscal, and labral injuries [18]. Furthermore, a meta-analysis of 18 clinical studies conducted by Fitzpatrick et al. found strong evidence that the use of leukocyte rich PRP (LR-PRP) stimulates tendon repair in upper limb tendinopathies [19]. Mechanistically, these findings support the "failed healing" pathophysiological hypothesis of tendon pain, whereby the use of PRP can potentially restart the stalled tissue healing mechanisms that underpin chronic shoulder pain [20]. Specifically, because PRP modulates the inflammation process and initiates the influx of factors that activate and differentiate endogenous stem cells, platelet-rich plasma is proving to be a valuable element in a broader, integrated shoulder pain treatment protocol [20]. In another study of PRP for partial rotator cuff tears, patients' pain subsided after injection and their range of motion also improved significantly [21]. Finally, the two main outcome measures undergirding the PRP literature are pain relief and patient self-reported pain scores, both of which are invoked in our study [20].

Due to the difficulty in diagnosing a patient's shoulder pain generator, our approach is to regenerate the entire shoulder, including, but not limited to the rotator cuff tendons, the glenoid and acromioclavicular joints, the labrum, ligaments, and the subdeltoid bursa depending on a patient's condition. By strengthening these anatomical areas, we believe we may provide patients with an effective noninvasive procedure for sustained pain relief. The goal of our study was to determine the clinical efficacy of PRP treatments for a variety of musculoskeletal conditions that cause unresolved shoulder pain. To that end, we hope to establish a less invasive, lower risk, higher efficacy alternative to surgery that alleviates pain localized within the shoulder region.

Methods

Patients

This study is a longitudinal report of a clinical practice patient outcomes in which variables were tracked prospectively and data was analyzed retrospectively. Patients included in this study underwent a series of one to seven PRP treatments for shoulder pain at a solo practitioner private practice from July 2016 to May 2018. MRI findings were obtained and all treatments were prescribed on an individual basis, as recommended by a physician. Written informed consent was obtained prior to each treatment. MRI findings in addition to physical examination by our physician were used to diagnose patients' pain. These included glenohumeral osteoarthritis, rotator cuff tears, tendinosis, tendinitis, and labral tears. There were 12 patients without an MRI who were categorized as "Undiagnosed Musculoskeletal Pain." The cohort of patients were placed into three groups for data analysis depending on the number of treatments received. Group 1 received 1 treatment, group 2 received a series of 2 treatments, and group 3 received a series of 3 or more treatments.

As stated in our previous publications [22] when a patient at our clinic requires multiple treatments, we direct them to receive injections approximately fourteen days apart. Due to scheduling conflicts, however, injection intervals tend to be greater than fourteen days. At the fourteen day mark following treatment, there is growth factor secretion from various cell types that participate in the late phases of wound healing [23,24]. Patients were also instructed not to use anti-inflammatory drugs during treatment, as they negate platelet function [25]. For patients who underwent bilateral shoulder treatment, each shoulder was given a separate survey and thus considered separately for statistical analysis. Patients characteristics can be found in **Table 1**.

Procedure

48-cc of blood was drawn into six 8.5mL ACD solution A tubes. The blood was then spun in a centrifuge, and the top layer without visible red blood cells was isolated to yield 12-cc PRP. The PRP was then split into 4-cc portions and was added to three 6-cc syringes. 2-cc of Lidocaine was added to each syringe to ensure less post-injection stiffness. The injection sites were sterilized with 4% Hibiclens. The PRP was injected by the physician into shoulder joint, and labrum under ultrasound guidance with a 2 inch 25 gauge needle, and then into the supraspinatus, infraspinatus, teres minor, and subdeltoid bursa depending on the patient's pain and pathology determined by our physician.

Out comes

The variables measured in this study, as seen in **Figure 1**, were changes to resting and active pain, total overall improvement percentage, and a modified upper extremity functionality scale. The functionality portion of the questionnaire, which assessed degree of difficulty in performing daily activities, was based on 10 of 20 activities assessed in the Upper Extremity Functional Index, [26] but also included a "not applicable (N/A)" response option. This scale has shown to be a valid and reliable functionality questionnaire for upper extremity limbs.[24] The Numerical Pain Scale was used to measure resting and active pain used a scale of 0 (no pain) to 10 (extreme pain) [27]. Lastly, the form included a subjective measure of how much overall improvement the patient experienced following treatment on a scale of 0% to 100%. These variables were measured at baseline and at 1 month, 3 month, 6 months, and annually after the first treatment.

Column1	N	
Age	52	56.72 (14.18)
BMI	52	25.77 (4.87)
Gender %		
Male	30	57.69%
Female	22	42.31%
Pathology of Shoulder Pain (N= 61 Shoulders)		
Rotator Cuff Tear	15	24.59%
Glenohumeral Osteoarthritis	24	39.34%
Tendinosis	5	8.20%
Tendonitis	2	3.28%
Undiagnosed Musculoskeletal Pain	12	19.67%
Labrum Tear	3	4.92%

Table 1 : Patient Characteristics

Upper Extremity Functionality Questions

Please describe the degree of difficulty you have while performing these activities with your injured upper body part.

	Activities	Extreme Difficulty	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty	N/A
1	Job, housework, or school activities	0	1	2	3	4	N/A
2	Hobbies, recreational, or sport activities	0	1	2	3	4	N/A
3	Lifting a heavy box	0	1	2	3	4	N/A
4	Opening a door	0	1	2	3	4	N/A
5	Washing dishes	0	1	2	3	4	N/A
6	Rolling over in bed	0	1	2	3	4	N/A
7	Carrying a heavy object	0	1	2	3	4	N/A
8	Combing/brushing your hair	0	1	2	3	4	N/A
9	Raising your arm over your head	0	1	2	3	4	N/A
10	Putting on and taking off a shirt	0	1	2	3	4	N/A

Total:

Resting Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Active Pain Level: 0 (No pain) 1 2 3 4 5 6 7 8 9 10 (Extreme pain)

Improvement Since Date of First Treatment (%): 0 10 20 30 40 50 60 70 80 90 100

Figure 1 : Patient Questionnaire

Statistical analysis

Each follow-up response was compared to its corresponding baseline response using the Wilcoxon signed-rank test. Post-interventional data between treatment groups were compared using the Wilcoxon sum-rank test. Responses per shoulder were assumed independent for analytic purposes. Statistical significance was set at *P* less than 0.05 and statistical analysis was performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, there were 61 shoulders that underwent 133 treatments. There were four patients who underwent bilateral treatment in the first group, two patients who underwent bilateral treatment in the second group, and three patients who underwent bilateral treatment in the third group. In Group 3, there were 12 shoulders that received three treatments, two shoulders that received four treatments, and three shoulders that received seven treatments. The second group underwent treatment 20.22 days apart and the third group underwent treatment 20.00 days apart. Patient results can be found in Tables 2 - 4 and Figure 2

Between groups, patients experienced successive decreases in resting and active pain with the increased amount of treatments. Group 2 reported a 1.13 (P=0.007) decrease in resting pain, which is a 50.94% decrease compared to baseline and Group 3 reported a 2.24 (P=0.001) decrease in resting pain, which is a 62.30% decrease compared to baseline. Group 3 showed superior outcomes in terms of resting pain compared to Group 1. In terms of active pain, Group 1 reported a 1.65 (P=0.022) decrease, Group 2 reported a 2.25 decrease, and Group 3 reported a 3.35 (P=0.001) decrease. That is a 25.19%, 32.53% and 48.31% respective decrease in active pain compared to baseline.

When patients were asked how much overall improvement they had experienced, there was also successive increases with additional treatments. The first group experienced 38.35% over-

Number of Treatments	0	1	Difference	P-Value	Percent Difference
Resting Pain (0-10)	**3.05**	**2.55**	**0.5**	**0.18**	**16.39%**
Mean (SD)	**-3**	**-2.32**			
Active Pain (0-10)	**6.55**	**4.9**	**1.65**	**0.022**	**25.19%**
Mean (SD)	**-2.26**	**-2.69**			
Total Improvement (0-100%)	-	**38.35%**			**38.35%**
Mean (SD)		**-34.64**			
Functionality Score (0-40)	**21.15**	**25.4**	**4.25**	**0.014**	**20.09%**
Mean (SD)	**-8.07**	**-7.47**			
Follow up Time (mo.)	**4.79**				

Table 2 : The Baseline and Post-Treatment Scores of Patients who received 1 PRP Treatments for Unresolved Shoulder Pain. N=20 Shoulders

Resting Pain (0-10)	**2.21**	**1.08**	**1.13**	**0.007**	**50.94%**
Mean (SD)	**-2.32**	**-1.41**			
Active Pain (0-10)	**6.92**	**4.67**	**2.25**	**0.001**	**32.53%**
Mean (SD)	**-1.81**	**-2.55**			
Total Improvement (0-100%)	-	**48.33%**			**48.33%**
Mean (SD)		**-36.88**			
Functionality Score (0-40)	**20.92**	**26.38**	**5.46**	**0.001**	**26.10%**
Mean (SD)	**-7.8**	**-9.04**			
Follow up Time (mo.)	**6.97**				
Days between Injections	**20.22**				

Table 3. The Baseline and Post-Treatment Scores of Patients who received 2 PRP Treatments for Unresolved Shoulder Pain. N=24 Shoulders

Number of Treatments	0	03-Jul	Difference	P-Value	Percent Difference
Resting Pain (0-10)	**3.59**	**1.35**	**2.24**	**0.001**	**62.30%**
Mean (SD)	**-2.69**	**-2.34**			
Active Pain (0-10)	**6.94**	**3.59**	**3.35**	**0.001**	**48.31%**
Mean (SD)	**-2.19**	**-2.87**			
Total Improvement (0-100%)	-	**55.53%**			**55.53%**
Mean (SD)		**-38.39**			
Functionality Score (0-40)	**19.65**	**27.82**	**8.18**	**0.001**	**41.62%**
Mean (SD)	**-9.15**	**-7.82**			
Follow up Time (mo.)	**7.38**				
Days Between Injections	**20**				

Table 4. The Baseline and Post-Treatment Scores of Patients who received 3 or more PRP Treatments for Unresolved Shoulder Pain. N=17 Shoulders

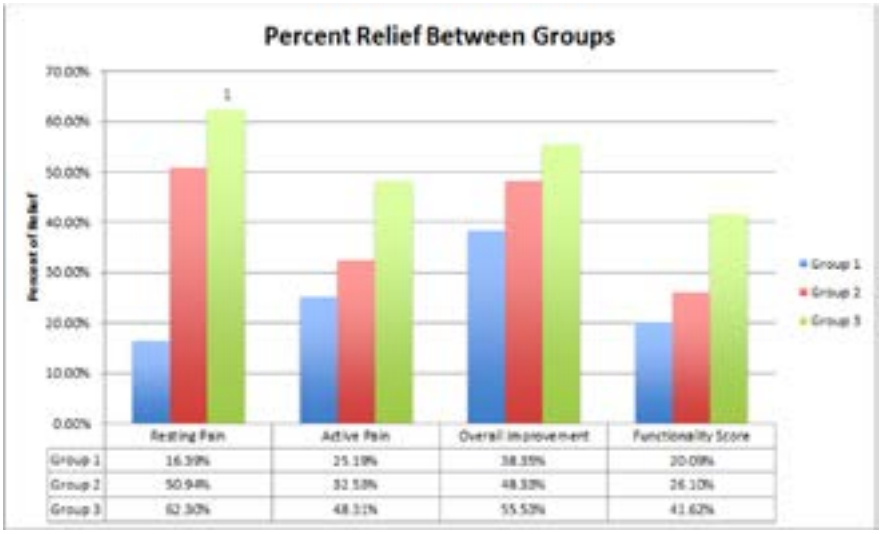

Figure 2 : Percent Relief Between Treatment groups

1-Statistically significant (P < .05) compared with outcomes after first injection.

all improvement, the second group experienced 48.33% overall improvement, and the third group experienced 55.53% overall improvement. 31 out of 61 shoulders included in this study experienced at least 50% total overall improvement compared to their condition prior to treatment.

Patients in each group were able to perform daily activities with less difficulties after treatment. Group 1 experienced a 4.25 (P=0.014) increase in functionality score, which is a 20.09% increase compared to baseline. Group 2 experienced a 5.46 (P=0.001) increase in functionality score, which is a 26.10% increased compared to baseline. Group 3 experienced a 8.18 (P=0.001) increase in functionality score, which is a 41.62% increase compared to baseline.

Discussion

All treatment groups in our study experienced mean reductions in resting and active shoulder pain as well as increased shoulder functionality as measured by the joint function questionnaire. Patients experienced a statistically significant improvement in active pain and functionality score after a single PRP treatment. These same patients who received one treatment experienced improvements in resting pain, yet were not statistically significant. Our results indicated significant improvement in all measurable outcomes for shoulder pain and function after a series of two treatments and continued improvement after a series of three or more treatments.

These findings show clinical relevance as they indicate that PRP operates through a number of the physiologic pathways that cause shoulder pain. Based on the downward trend of pain symptoms observed after each series of PRP treatment in this study, we hypothesize that the successive rounds of PRP have an additive effect as cellular and humoral mediators of pain accumulate in-situ. This is reflected in the fact that our results indicate significant improvement in all measurable outcomes for shoulder pain and function after two treatments and continued improvement after three treatments. To that end, our observation that improvement of resting shoulder pain was not statistically significant until two PRP treatments is consistent with the idea that a threshold level of molecular recruitment is required to reach clinically measurable effects.

Traditional treatments other than surgery for unresolved shoulder pain include corticosteroid interventions, however the evidence for their efficacy is lacking and insufficient. For example, a Cochrane Library review of 26 randomized controlled trials of corticosteroid injections for shoulder pain concluded that subacromial corticosteroid injections yielded marginal and short lived benefits for patients [28]. These findings are echoed in the FDA's 2014 drug safety warning, which indicates that the effectiveness of steroid use for joint pain has not been robustly established and that there is potential for serious adverse effects. As a result, it behooves clinicians and researchers to investigate and employ treatment modalities for shoulder pain that are effective, lasting, and possess safety profiles that are superior to intra-articular steroid injections.

Prolotherapy is one such proposed therapy. At concentrations exceeding 10%, hypertonic dextrose prolotherapy administered to the shoulder joint creates a local osmotic gradient, causing cell lysis, initiating both a beneficial inflammatory response and the influx of growth factors that assist in the deposition of new collagen, strengthening nearby ligaments [29]. A double-blind placebo study found that dextrose prolotherapy outperformed a control group in terms of pain and quality of life in patients with chronic shoulder pain [30]. In comparative studies, however, PRP therapy was found to produce superior improvement as well as more consistent and lasting pain relief than dextrose prolotherapy treatment [31]. In fact, the capacity for PRP to enhance the tendon repair process in shoulder joints has been borne in a number of clinical studies and animal experiments, especially in patients with small to medium rotator cuff tears [32-37]. Platelet-rich plasma therapy is hypothesized to yield better

clinical outcomes than dextrose prolotherapy because it contains high concentrations of autologous platelet-derived growth factors that can stimulate the healing process [31]. Clinicians can also use high-yield PRP preparations that contain concentrated white blood cells derived from the buffy coat, leukocyte-derived antibacterial agents and additional growth factors that can hasten initiation of the healing process [31].

Additionally, there is great potential for PRP when combined with and administered in parallel with other compounds to yield synergistic effects on shoulder pain and function. A 2018 study conducted by Cai et al. examined the effect of a PRP preparation that was supplemented with sodium hyaluronate (SH), a compound that is present in the extracellular matrix of connective tissue and is a component of synovial fluid [38]. The combined PRP and SH solution at a 2:1 volumetric ratio was found to be superior to either PRP or SH alone. This included the improvement in healing of partial-thickness rotator cuff tears, which account for 20-40% of shoulder joint diseases [38]. While SH does not act on the degenerative process of the rotator cuff in the same mechanism as PRP per se, it is hypothesized that SH can increase the residence time of the growth factors within PRP, thereby facilitating the molecular diffusion of anti-inflammatory and pain mediating compounds [38]. Further research into the use of PRP will not only enhance our understanding of potentially beneficial interactions with other treatments, but also assist in the widespread adoption of this minimally invasive treatment for patients who have not responded to traditional treatments.

The limitations of our study include the nature of unresolved shoulder pain itself. According to epidemiologic studies, the pathology underlying persistent shoulder pain is typically multifactorial and diverse, ranging from bursitis to avascular necrosis and several permutations in between [39]. This is of consequence because it is conceivable that the patients with the most complex shoulder pain etiologies in this study were precisely those who necessitated more than one PRP treatment to yield significant resting pain relief, i.e., did not demonstrate significant pain relief after only one PRP treatment . Finally, the subjectivity of the measured variables may have introduced response bias. Further randomized-controlled studies with larger sample sizes and longer follow-ups are warranted to further validate these results.

Conclusion

Patients experienced improvements in pain and function after one PRP treatment and continued to experience increased benefit with subsequent number of injections. These results are encouraging and warrant further randomized-controlled trials to confirm the validity of PRP therapy for shoulder pain.

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