Original Article

Clinical Results of Platelet-Rich Plasma in Frozen Shoulder

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Abstract

Background: Frozen shoulder is a common cause of shoulder pain and disability. Several treatments are utilized to reduce patients' pain and improve range of motion (ROM). Recent researches have been conducted on Platelet-rich plasma (PRP) injection. In this study, the clinical results of PRP injection for patients with frozen shoulder was assessed.

Materials and Methods: Forty-four patients in phases I or II of frozen shoulder were treated with PRP. During the first session, two syringes of PRP were injected in the subacromial bursa and intra-articular space; this process was repeated after four weeks. In the second stage, PRP was injected only in the glenohumeral joint.

Results: The average pre-treatment flexion was about 65°; abduction was 70°while external rotation was 22°. Also, baseline scores for VAS, DASH, and SF-12 Health Survey questionnaire were 8.4, 65.9 and 26, respectively. After 25 weeks follow-up, all patients showed significant improvement in shoulder ROM, pain, and function ($p<0.001$). Patients reported 66.7% improvement in pain, 51.6% in DASH score, and 100% in SF-12 Health Survey questionnaire. They were also 65% satisfied with the treatment protocol.

Conclusion: This case series study demonstrated clinically and statistically significant improvement in patients' pain and disability outcomes following PRP injection. These results provide support for PRP as a safe treatment protocol that decreases pain and increases upper limb function. In addition, it can also improve shoulder range of motion.

Keywords: Frozen shoulder, Adhesive capsulitis, Platelet-rich plasma, PRP injection

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Introduction

Adhesive capsulitis or frozen shoulder is a common cause of shoulder pain and disability and is estimated to affect between 2 and 5% of the general population with peaks between 40 and 70 years of age (1, 2). It is defined by a spontaneous onset of pain with progressive stiffness of the glenohumeral joint (because of adhesion and fibrosis in the joint capsule) which can lead to limitation in gross function, especially loss of external rotation. The causes of this disease are not fully understood. Some medical problems associated with frozen shoulder include diabetes, hypothyroidism, hyperthyroidism,

Parkinson's disease, and cardiac disease (1, 3, 4).

Adhesive capsulitis typically occurs in three phases: Phase I - the 'freezing' painful phase, which lasts for about 2-9 months; Phase II - the 'frozen' or stiff (or adhesive) phase, which lasts 4-12 months. In this phase muscles around the shoulder may waste a bit as they are not used; Phase III - the 'thawing' or recovery phase which lasts between one and three years. After this phase, the pain and stiffness gradually disappear and movement gradually returns to normal, or near normal (5, 6). In minority of patients, symptoms last for several years; up to 40% of patients have permanent symptoms after three years (7, 8)

Several treatments are utilized to reduce patients' pain and improve range of motion (ROM). These treatments, in isolation or combined, include intra-articular injections, nerve block, shoulder manipulation under anesthesia, mobilization and passive stretching exercises, oral NSAIDs (non steroidal anti-inflammatory drugs) and analgesics, and open or arthroscopic surgery with synovectomy and glenohumeral capsular releases (6, 9).

Recent researches have been conducted on platelet-rich plasma (PRP) injection is a concentrated source of autologous platelets in blood plasma which contains several different growth factors and other cytokines that can stimulate healing of soft tissue (10, 11). PRP is a safe and effective form of treatment in the field of dermatology, orthopedics and dentistry. Platelet-rich plasma can produce collagen and growth factors and might increase stem cells, and consequently enhance the healing process by delivering high concentrations of alpha-granules containing biologically active moieties (such as vascular endothelial growth factor and transforming growth factor-β) to the areas of soft tissue damage (3, 12-14).

PRP therapy has shown good results for lesions in tendons, muscles and ligaments and even fractures; and there is no evidence of complications related to its application (12, 13, 15). Since only one case study had investigated the effect of PRP injection in patients with frozen shoulder (3) and due to the lack of sufficient evidence in this field, the purpose of this case series study was to investigate the clinical results of PRP injection in patients with frozen shoulder, at an average follow up duration of 25 weeks.

Methods

The study was approved by the Ethics in Research Committee, SBMU, Tehran, Iran; ethics code: IR.SBMU.RETECH.REC.1399.415. Written informed consent was also obtained from all patients.

Forty-four patients (30 women and 10 men) in phase I or II of frozen shoulder, with a mean age of 52.3 years were treated with PRP (Table 1). All cases suffered from at least 1 month of shoulder pain, especially at night, followed by gradual loss of both active and passive range of motion (subjects had a decreased passive range of motion of 20% or more, in at least three motions according to the American Medical Association guide for the evaluation of permanent impairment (16). After plain radiography and MRI, frozen shoulder was confirmed in patients and other causes of shoulder pain ruled out. Exclusion criteria were:

- adhesive capsulitis due to a secondary etiology, or due to trauma with long time of immobilization cerebrovascular accident, or fractures
- any known blood coagulation disorder
- any history of previous injection in the involved shoulder

Treatment and experimental protocol

All stages of the PRP preparation were performed according to a standardized protocol as per the device's manufacturer's specifications (Arthrex-ACP (Autologous Conditioned Plasma). At the beginning, 2×15cc of the patients' blood was drawn from the superficial saphenous vein with a double syringe (Arthrex-ACP system). Subsequently, the blood sample was centrifuged at 1500 rpm for five minutes to separate the blood into layers of red blood cells, buffy-coat of leucocytes, and plasma and finally, PRP was collected. First, two syringes of PRP in the sub acromial bursa and intra-articular space (2cm below the posterolateral of the acromion and 2cm towards the medial). Then this process was repeated after four weeks. In this stage, PRP was injected only in the glenohumeral joint. Home shoulder stretching exercise program was emphasized to the patient after every injection (no type of physical therapy). Patients' visit was performed at 4 weeks (second injection), intervals for 6 and 25 weeks. Baseline data were obtained immediately before the first injection and

follow-up data at 25 weeks after the second injection. Passive shoulder abduction, flexion and external rotation were measured using the goniometer. Pain was evaluated using the visual analogue scale (VAS) (with 0 indicating no pain and 10 indicating the worst possible pain). The Persian version of the disability of the arm, shoulder and hand (DASH) questionnaire and SF-12 health survey questionnaire were used to assess functional condition (2, 3). Finally, the patients were asked about their degree of satisfaction using the Likert scale. Data analyses were done using the SPSS software for Windows, version 18 (SPSS Inc., Chicago IL). A p-value of less than 0.05 was considered to be significant. The Kolmogorov Smirnov test was used to assess the normality of the data while paired sample t-test (for normal data) and Wilcoxon rank sum test (for non-parametric data) were used to compare mean difference between before and after injection administration.

Results

Forty-four patients, aged 39 to 67 years (77.3% female; 22.7% male) who underwent PRP injection for the treatment of frozen shoulder (61.4% left affected limb, 38.6% right affected limb) were included in the analysis after 25 weeks' follow-up. For each outcome, the mean and standard deviation before and after injection are summarized in Table 2. The average pre-treatment flexion was about 65°, abduction was 70° and external rotation was 22°. In addition, baseline scores for VAS, DASH, and SF-12 Health Survey questionnaire were 8.4, 65.9 and 26, respectively. After 25 weeks follow-up, all patients showed significant improvement in shoulder ROM, pain, and function ($p<0.001$) (Table 2). Patients reported 66.7% improvement in pain, 51.6% in DASH score, and 100% in SF-12 Health Survey questionnaire. They were also 65% satisfied with the treatment protocol.

Discussion

Frozen shoulder syndrome or adhesive capsulitis, is a painful and disabling disease considered as fibrosis of the glenohumeral joint capsule with a chronic inflammatory reaction (17, 18). Patients suffer from pain, limited range of motion, and disability usually lasting anywhere from 1 to 24 months (18).

This disease remains an unresolved clinical condition. No present treatment protocols are generally impressive, and there is a great need for further research and improvement of more effective treatment

Table 1: Patient characteristics.

Frozen shoulder stage (I/II)	Side of effect (L/R)	Age(year) (Mean ± SD)	Gender (M/F)
54.5% / 45.5%	38.6% / 61.4%	52.3±7.2	22.7% / 77.3%

Table 2: Comparison of patient's outcomes before and after PRP injections.

Variables	Before Injection		After Injection		P Value
	Mean	Std. Deviation	Mean	Std. Deviation	.000
Abduction ROM(º)	70.3409	36.15403	139.7500	9.99331	.000
Flexion ROM(º)	65.0455	9.55755	147.9773	11.37621	.000
External rotation ROM	21.8864	3.71806	48.0455	9.55511	.000
VAS	8.4091	1.08517	2.7955	1.21195	.000
DASH	65.8636	5.17413	31.8636	7.31227	.000
SF12	26.0000	5.85880	69.1591	11.75910	.000

ROM (range of motion), Visual analogue scale (VAS), Disability of Arm, Shoulder and Hand (DASH) questionnaire.

protocols. Morbidity from this disease has individual and social costs, and if treatment and management are not constant, disability is long-lasting (17, 19).

Using corticosteroid and hyaluronic acid injections for conservative treatment of adhesive capsulitis could give pleasing outcomes; also some physicians recommend physical therapy (20). Some results show that intra-articular corticosteroid injections provide better short-term pain relief and improved range of motion compared with oral glucocorticoid therapy in patients with adhesive capsulitis (21, 22). Some studies have reported the superiority of physical therapy to hyaluronic acid and corticosteroid injections (9, 23). On the contrary, one study reported that hyaluronic acid injections did not produce great benefits for patients with frozen shoulder who were receiving physiotherapy (24). Systematic reviews on this subject have not yet confirmed the superiority of physiotherapy or other treatments (25, 26). Some studies show that using occupational therapy assisted in pain management and disability in conjunction with corticosteroid injections. Thus, the treatment regimen was more effective than physical therapy alone (2). Another study reported that no major differences between corticosteroid alone and in combination with hyaluronic acid in patients with frozen shoulder after 6 months follow up. In addition, they recommended that patients who were receiving regular conventional treatment should be evaluated for side effects (26, 27).

Since the late 1980s when platelet concentrates were used as topical therapy to treat chronic leg ulcers, their use has been extended to many medical fields such as chronic elbow tendinopathy, chronic Achilles tendinopathy, and rotator cuff tendon tears with the aim of controlling inflammatory reaction and improve tissue healing and regeneration (28, 29). The complete mechanisms by which PRP initiates cellular and tissue changes are now being investigated. It is clear that PRP induces multiplication of a variety of cell types and has been found to recruit reparative cells. Connective tissue healing occurs in three phases: inflammation, proliferation, and remodeling. The unique combination and concentration of bioactive molecules that exist within PRP have deep effects on the inflammatory, proliferative, and remodeling phases of tissue healing (3, 15). This explains why PRP injection can have a lasting effect on the healing process. Through interaction with macrophages, PRP may control the inflammatory reaction and thus progress tissue healing and regeneration (14, 29). The results of this trial show that PRP injection, coupled with a simple home stretching exercise program, is successful in treating (that is, improving shoulder pain and function at 25 weeks) patients with adhesive capsulitis of the shoulder. Physicians generally recommend corticosteroid and hyaluronic injections or physiotherapy for treating frozen shoulder, but such protocols have some side effects, and physiotherapy has not showed a superior efficacy according to the literature (1, 26). However, in this case series study we have introduced a new effective intervention for improvement, which seems to have no side effects.

Conclusion

This case series including 44 cases who were in the phase I or II of frozen shoulder to suitable conservative therapy demonstrated clinically and statistically significant improvement in patients' pain and disability outcomes following PRP injection. These results provide support for PRP as a safe treatment protocol that decreases pain and increases upper limb function. In addition, it can improve shoulder range of motion. Randomized controlled trials with longer follow-up and comparing the efficacy of corticosteroids, hyaluronic acid, and physiotherapy with PRP are supported to further investigate the influence of PRP injection for the treatment of frozen shoulder.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Blanchard V, Barr S, Cerisola FL. The effectiveness of corticosteroid injections compared with physiotherapeutic

interventions for adhesive capsulitis: a systematic review. Physiotherapy. 2010;96(2):95-107.
2. Ewald A. Adhesive capsulitis: a review. Am Fam Physician. 2011;83(4):417-22.
3. Aslani H, Nourbakhsh ST, Zafarani Z, Ahmadi-Bani M, Ananloo ME, Beigy M, et al. Platelet-Rich Plasma for Frozen Shoulder: A Case Report. Arch Bone Jt Surg. 2016;4(1):90-3.
4. Kobayashi T, Karasuno H, Sano H, Hamada J, Takase K, Tamai K, et al. Representative survey of frozen shoulder questionnaire responses from the Japan Shoulder Society: What are the appropriate diagnostic terms for primary idiopathic frozen shoulder, stiff shoulder or frozen shoulder? J Orthop Sci. 2019;24(4):631-5.
5. Jain TK, Sharma NK. The effectiveness of physiotherapeutic interventions in treatment of frozen shoulder/adhesive capsulitis: a systematic review. J Back Musculoskelet Rehabil. 2014;27(3):247-73.
6. Neviaser AS, Hannafin JA. Adhesive capsulitis: a review of current treatment. Am J Sports Med. 2010;38(11):2346-56.
7. Hand C, Clipsham K, Rees JL, Carr AJ. Long-term outcome of frozen shoulder. J Shoulder Elbow Surg. 2008;17(2):231-6.
8. Shaffer B, Tibone JE, Kerlan RK. Frozen shoulder. A long-term follow-up. J Bone Joint Surg Am. 1992;74(5):738-46.
9. Harris JD, Griesser MJ, Copelan A, Jones GL. Treatment of adhesive capsulitis with intra-articular hyaluronate: A systematic review. Int J Shoulder Surg. 2011;5(2):31-7.
10. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. 2004;114(6):1502-8
11. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. Am J Sports Med. 2013;41(1):186-93.
12. Gautam VK, Verma S, Batra S, Bhatnagar N, Arora S. Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: clinical and ultrasonographic evaluation. J Orthop Surg (Hong Kong). 2015;23(1):1-5.
13. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62(4):489-96.
14. Zafarani Z, Mirzaee F, Guity M, Aslani H. Clinical Results of Platelet-Rich Plasma for Partial Thickness Rotator Cuff Tears: A Case Series. Arch Bone Jt Surg. 2017;5(5):328-31.
15. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg. 2009;17(10):602-8.
16. Noben CY, Evers SM, Nijhuis FJ, de Rijk AE. Quality appraisal of generic self-reported instruments measuring health-related productivity changes: a systematic review. BMC Public Health. 2014;14:115.
17. Brue S, Valentin A, Forssblad M, Werner S, Mikkelsen C, Cerulli G. Idiopathic adhesive capsulitis of the shoulder: a review. Knee Surg Sports Traumatol Arthrosc. 2007;15(8):1048-54.
18. Page P, Labbe A. Adhesive capsulitis: use the evidence to integrate your interventions. N Am J Sports Phys Ther. 2010;5(4):266-73.
19. Buchbinder R, Green S, Youd JM, Johnston RV, Cumpston M. Arthrographic distension for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2008(1):Cd007005.
20. Laska T, Hannig K. Physical therapy for spinal accessory nerve injury complicated by adhesive capsulitis. Phys Ther. 2001;81(3):936-44.
21. Lorbach O, Anagnostakos K, Scherf C, Seil R, Kohn D, Pape D. Nonoperative management of adhesive capsulitis of the shoulder: oral cortisone application versus intra-articular cortisone injections. J Shoulder Elbow Surg. 2010;19(2):172-9.
22. Carette S, Moffet H, Tardif J, Bessette L, Morin F, Frémont P, et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder: a placebo-controlled trial. Arthritis Rheum. 2003;48(3):829-38.
23. Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int. 2006;26(6):536-40.
24. Hsieh LF, Hsu WC, Lin YJ, Chang HL, Chen CC, Huang V. Addition of intra-articular hyaluronate injection to physical therapy program produces no extra benefits in patients with adhesive capsulitis of the shoulder: a randomized controlled trial. Arch Phys Med Rehabil. 2012;93(6):957-64.
25. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
26. Uppal HS, Evans JP, Smith C. Frozen shoulder: A systematic review of therapeutic options. World J Orthop. 2015;6(2):263-8.
27. Rovetta G, Monteforte P. Intraarticular injection of sodium hyaluronate plus steroid versus steroid in adhesive capsulitis of the shoulder. Int J Tissue React. 1998;20(4):125-30.
28. Knighton DR, Doucette M, Fiegel VD, Ciresi K, Butler E, Austin L. The use of platelet derived wound healing formula in human clinical trials. Prog Clin Biol Res. 1988;266:319-29.
29. Mishra A, Woodall J, Jr., Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med. 2009;28(1):113-25.