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Original Article

Effects of platelet-rich plasma injection on pain, range of motion, and disability in adhesive capsulitis: A prospective, randomized-controlled study

Çağlar Karabaş[1], Havva Talay Çalış[1], Ulaş Serkan Topaloğlu[2], Çiğdem Karakükçü[3]

[1]Department of Physical Medicine and Rehabilitation, Kayseri City Hospital, Kayseri, Turkey
[2]Department of Internal Medicine, Kayseri City Hospital, Kayseri, Turkey
[3]Department of Biochemistry, Kayseri City Hospital, Kayseri, Turkey

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ABSTRACT

Objectives: In this study, we aimed to investigate the effectiveness of intra-articular platelet-rich plasma (PRP) injection in adhesive capsulitis.

Patients and methods: Between January 2019 and December 2019, a total of 40 patients (21 males, 19 females; mean age: 57.1±6.5 years; range, 44 to 72 years) with idiopathic adhesive capsulitis were included. The patients were randomly assigned into two equal groups as the PRP and the control group. The PRP group received two doses of PRP via intra-articular route biweekly under ultrasound guidance. No injection was performed to the control group. In both groups, stretching and Codman exercises were applied as a home-based program. The Visual Analog Scale (VAS), range of motion (ROM), and Shoulder Pain and Disability Index (SPADI) scores were evaluated before the treatment and at 2, 6 and 12 weeks after the treatment.

Results: There were significant differences in all VAS, SPADI, and ROM scores at all time points after treatment compared to baseline in both groups. At the end of the study, there were significant differences in the active flexion, passive flexion, active abduction, passive abduction, and active external rotation scores at 12 weeks between the groups (p=0.012, p=0.015, p=0.008, p=0.019, and p=0.040, respectively). No significant difference was observed between the groups in terms of VAS and SPADI scores and the other parameters (active and passive extension, active and passive internal rotation, passive external rotation) at 2, 6, and 12 weeks (p>0.05).

Conclusion: The addition of PRP to exercise treatment can improve patients' joint mobility, but not pain and disability in patients with adhesive capsulitis.

Keywords: Adhesive capsulitis, disability, pain, platelet-rich plasma, range of motion.

Adhesive capsulitis, also known as frozen shoulder, defines a pathological process characterized by adhesion or excessive scarring in the glenohumeral joint, which causes stiffness, pain, and dysfunction in the shoulder.[1,2] Adhesive capsulitis, which is considered that a large number of growth factors within the plasma content would increase tendon and cartilage tissue regeneration, is seen in the general population at a rate of approximately 3 to 5%.[3] The clinical picture indicates a tendency to spontaneous recovery within one to three years. However, it demonstrates a resistant process in 20 to 40% of cases.[2,3]

Platelet-rich plasma (PRP) obtained by centrifugation of whole blood is the plasma component that contains a higher platelet concentration than whole blood.[4] Histopathological evidence shows that

Corresponding author: Ulaş Serkan Topaloğlu, MD. Kayseri Şehir Hastanesi İç Hastalıkları Kliniği, 38080 Kocasinan, Kayseri, Türkiye.
e-mail: ustop38@gmail.com

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failure of repair mechanisms plays a role in the pathological process rather than inflammation in chronic soft tissue degeneration.[5] The fact that PRP contains many growth factors has led to the use of PRP injections in the treatment of several musculoskeletal system disorders.[6,7] It has been suggested that growth factors considered to play a role in the healing process can be potentially used in the treatment by enhancing their effects on tendon and cartilage tissue via local administration rather than lesions.[5] Although there are increasing numbers of clinical trials investigating PRP injections in musculoskeletal system disorders in the literature, the effectiveness results are controversial.[8-11] Similarly, for shoulder joints, numerous references are available regarding rotator cuff tendinopathy, bicipital tendinopathy, and the usage of PRP in superior labrum anterior-posterior lesions.[12-14]

Despite many studies on PRP treatment in various joint diseases, there are scarce comparative data on the use of PRP in adhesive capsulitis. In the present study, we aimed to investigate the effectiveness of PRP therapy in patients with adhesive capsulitis.

PATIENTS AND METHODS

This single-center, single-blind, parallel-group, prospective randomized-controlled, study was conducted at Physical Therapy and Rehabilitation outpatient clinic of Kayseri City Hospital between January 2019 and December 2019. A total of 61 patients aged between 18 and 75 years with shoulder pain for at least three months, 50% limitation in at least one direction of range of motion (ROM), a Visual Analog Scale (VAS) score of >5, who underwent physical examination by a single physiatrist and were diagnosed with idiopathic adhesive capsulitis were screened. The patients were randomly assigned into two groups (PRP and the control) by another physiatrist, using the sealed envelope method at the beginning of the application. Patients who received an injection within the prior three months in the relevant region, those who received physical therapy in the relevant region, those with local infection, those with systemic infection or inflammatory disease (rheumatoid arthritis, hepatitis), those with diabetes mellitus, those with a history of malignancy (hematological or non-hematological), pregnant women, and those on systemic steroid therapy were excluded. Also, those with a full-thickness rotator cuff tear and patients having previous shoulder surgery were excluded from the study. Only those with partial rotator cuff tear together with adhesive capsulitis and patients with bursitis and tendinopathy were included in the study. A total of 18 patients were excluded from the study, as they had adhesive

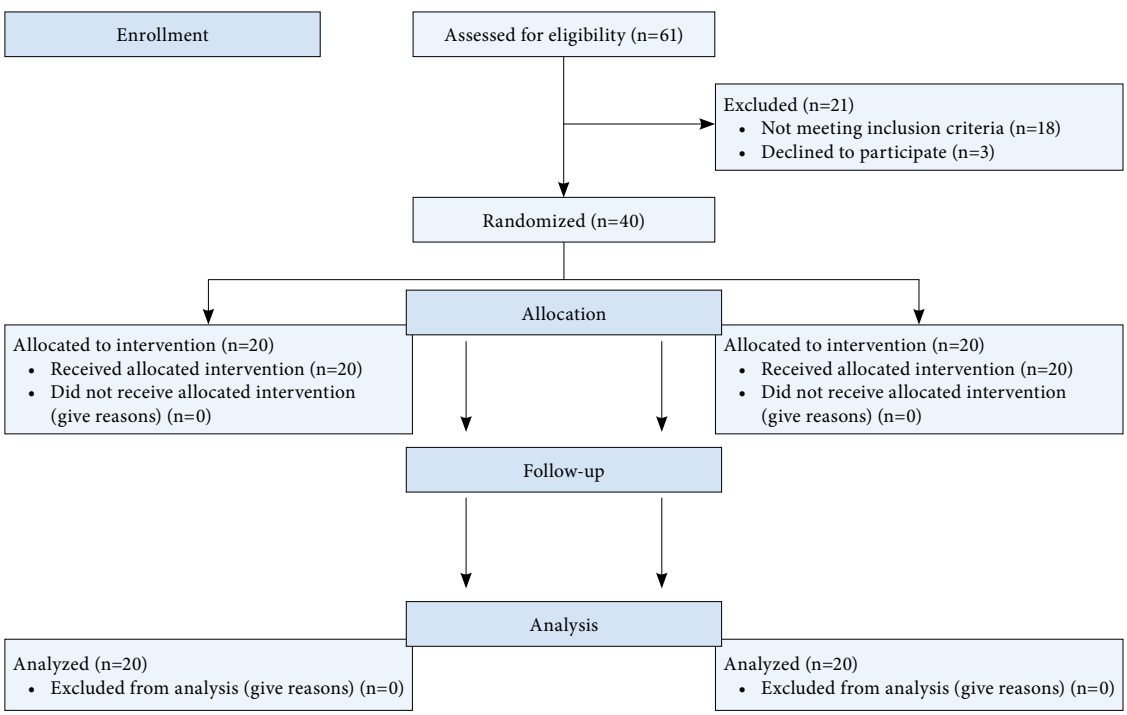

Figure 1. Study flow chart.

capsulitis due to secondary etiology. Three patients left the study due to the transportation problem. Finally, a total of 40 patients (21 males, 19 females; mean age: 57.1±6.5 years; range, 44 to 72 years) were included in the study. The study flow chart is shown in Figure 1.

A written informed consent was obtained from each patient. This study was approved by the Local Ethics Committee of Erciyes University Faculty of Medicine (No: 2017/272). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Using sonography guidance, two doses of PRP (3 mL) were injected biweekly into the glenohumeral joint via a posterior approach by a physiatrist blinded to the history and physical examination findings in 20 patients in the PRP group. No PRP injection was performed to the control one. Besides, a home-based exercise program including proprioceptive neuromuscular facilitation stretching and Codman pendulum exercises (3×10 repeats) was prescribed to all patients in the study. Moreover, the patients were asked not to use non-steroidal anti-inflammatory drugs until the end of the study, whereas paracetamol was allowed as an analgesic.

Preparation of platelet-rich plasma

Manual preparation techniques were used in the study.[15] In each patient, 24 mL of venous blood samples (8 mL × 3) were drawn into three sterile tubes containing 2 mL of anticoagulant citrate dextrose solution, from the cubital veins. The tubes were, then, centrifuged at 1,195 rpm for 20 min, resulting in three layers of whole blood sample: the first layer, plasma (superior layer); the second layer, buffy coat (platelets plus leukocytes); and the third layer, erythrocytes (inferior layer). The first and second layers were transferred to three empty tubes and re-centrifuged at 1,890 rpm for 15 min under laminar flow. This resulted in two layers. The first layer, the platelet poor superior layer was collected by syringe but was not used. The second layer was the platelet-rich inferior layer (1.5 mL per tube). From three tubes, 4.5 mL of PRP was obtained and divided into three tubes. Two tubes (3 mL) were used for treatment, while one tube (1.5 mL) was assigned for a platelet count to ensure the desired platelet count.

Ultrasound-guided intra-articular platelet-rich plasma injection technique

In the study, the glenohumeral joint was identified between the infraspinatus muscle and humeral head via a posterior approach by a Philips ClearVue 550 device (Philips Ultrasound Inc, Pennsylvania, USA), using a 512 Hz linear probe. Under appropriate sterile conditions, the intra-articular space was punctured by a 21-G needle. After confirmation of the needle tip within the intra-articular space, 3 mL of autologous PRP was administered into the capsule and the procedure was completed. The procedure was repeated two weeks after the first injection by the same physiatrist using the same technique. The injection procedure, randomization, and questionnaire were performed by different physiatrists.

TABLE 1
Sociodemographic and baseline characteristics of patients with adhesive capsulitis

Variables	PRP group (n=20)						Control group (n=20)						*p*
	n	%	Mean±SD	Median	IQR	25^{th}-75^{th} percentile	n	%	Mean±SD	Median	IQR	25^{th}-75^{th} percentile	
Age (year)			57.3±7.3						56.8±5.9				0.812
Sex													0.057
Female	6	30					13	65					
Male	14	70					7	35					
Height (cm)			163.8±7.2						167.2±7.0				0.137
Weight (kg)			77.0±12.0						78.1±11.2				0.765
BMI (kg/m^2)			28.9±5.1						28.1±4.5				0.594
Affected arm													0.999
Right	11	55					11	55					
Left	9	45					9	45					
Duration of symptoms (month)				6	5	3-8				3	4	3-7	0.149

PRP: Platelet-rich plasma; SD: Standard deviation; BMI: Body mass index; IQR: Interquartile range.

Outcome measures

Demographic characteristics of the patients were recorded. The pain was assessed by 10-points for VAS (0, no pain; 10, worst pain ever). In all patients, the pain was assessed separately as daytime pain (VAS-daytime), night pain (VAS-night), and during movement (VAS-movement).

In all patients, the Shoulder Pain and Disability Index (SPADI) was used to assess shoulder pain and disability by the same physiatrists. Pain and disability subscales were calculated as a mean value of items rated with a 0-100 scale, the highest scores indicating the most severe pain and disability. The SPADI, which is a scale used in adhesive capsulitis studies, is also a valid and reliable questionnaire in the Turkish population.[16,17]

The ROM was separately assessed as active and passive ROM (flexion, abduction, internal rotation, external rotation, extension).

TABLE 2
Non-parametric analysis of longitudinal data in factorial experiments for the VAS and SPADI scores

Source of variation	Wald	df	*p*
VAS pain score (day)			
Treatment	1.693	1	0.193
Time (week)	212.409	3	<0.001
Treatment x time (week)	3.676	3	0.299
VAS pain score (night)			
Treatment	1.525	1	0.217
Time (week)	142.226	3	<0.001
Treatment x time (week)	1.357	3	0.716
VAS pain score (motion)			
Treatment	0.001	1	0.985
Time (week)	185.157	3	<0.001
Treatment x time (week)	2.434	3	0.487
SPADI score (pain)			
Treatment	0.014	1	0.906
Time (week)	183.181	3	<0.001
Treatment x time (week)	2.606	3	0.456
SPADI score (disability)			
Treatment	0.011	1	0.915
Time (week)	231.528	3	<0.001
Treatment x time (week)	2.492	3	0.477
SPADI score (total)			
Treatment	0.021	1	0.884
Time (week)	239.002	3	<0.001
Treatment x time (week)	3.490	3	0.322

VAS: Visual Analog scale; SPADI: Shoulder Pain and Disability Index; df: Degrees of freedom.

The VAS-daytime, VAS-night, VAS-movement, active and passive ROM, SPADI-pain, SPADI disability, and SPADI-total were assessed at baseline and at 2, 6, and 12 weeks.

TABLE 3
Non-parametric analysis of longitudinal data in factorial experiments for the ROM scores

Source of variation	Wald	df	*p*
Flexion (active)			
Treatment	1.810	1	0.179
Time (week)	115.875	3	<0.001
Treatment x time (week)	5.612	3	0.132
Flexion (passive)			
Treatment	2.504	1	0.114
Time (week)	135.437	3	<0.001
Treatment x time (week)	5.041	3	0.169
Extension (active)			
Treatment	0.109	1	0.741
Time (week)	84.240	3	<0.001
Treatment x time (week)	3.208	3	0.361
Extension (passive)			
Treatment	0.094	1	0.759
Time (week)	140.782	3	<0.001
Treatment x time (week)	2.126	3	0.547
Abduction (active)			
Treatment	0.716	1	0.398
Time (week)	225.192	3	<0.001
Treatment x time (week)	11.908	3	0.008
Abduction (passive)			
Treatment	0.939	1	0.333
Time (week)	231.315	3	<0.001
Treatment x time (week)	11.285	3	0.010
Internal rotation (active)			
Treatment	0.037	1	0.846
Time (week)	163.217	3	<0.001
Treatment x time (week)	3.730	3	0.292
Internal rotation (passive)			
Treatment	0.012	1	0.913
Time (week)	142.250	3	<0.001
Treatment x time (week)	4.822	3	0.185
External rotation (active)			
Treatment	0.595	1	0.440
Time (week)	135.028	3	<0.001
Treatment x time (week)	7.892	3	0.048
External rotation (passive)			
Treatment	0.393	1	0.531
Time (week)	157.299	3	<0.001
Treatment x time (week)	7.247	3	0.064

ROM: Range of motion; df: Degrees of freedom.

Statistical analysis

Study power analysis was performed using the G*Power version 3.0.10 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany). The post-hoc power analysis was calculated based on the Cohen's d and partial eta-square effect size statistics. All these calculations are conducted using R 3.6.1 (www.r-project.org) statistical software.

Statistical analysis was performed using the TURCOSA (Turcosa Analytics Ltd. Co., www.turcosa.com.tr) and nparLD library of R 3.6.1 (www.r-project.org) software.[18] Histogram, q-q plots, and Shapiro-Wilk's tests were used to assess the data normality. The Levene test was used to test variance homogeneity. Normally distributed quantitative data were expressed in mean ± standard deviation (SD), while non-normally distributed data were expressed in median and interquartile range (IQR). Qualitative data were expressed in number and frequency. Pearson chi-square analysis was used for comparison of categorical variables. To identify the main and interaction effects of treatment and time points on VAS, SPADI and ROM scores, non-parametric analysis of longitudinal data in factorial experiments was carried out.[19] Wald-type statistics were calculated for testing treatment group and time effects, and interaction. Experimental results were given in Wald statistic, degrees of freedom and *p* values. Inter-group comparisons were performed using a two-sided independent samples t-test and Mann-Whitney U test. Intra-group comparisons were performed using one-way repeated measures analysis of variance (ANOVA) and Friedman tests. Bonferroni and Nemenyi tests were used simultaneously for multiple comparisons. A *p* value of <0.05 was considered statistically significant.

TABLE 4
Changes from baseline in the VAS scores between PRP and control groups

	PRP group (n=20)			Control group (n=20)				
VAS pain score	Median	IQR	25th-75th quartiles	Median	IQR	25th-75th quartiles	*p**	Post-power
Day								
Baseline	8.0[a]	5	5.3/10.0	7.0[a]	4	4.0/8.0	0.121	0.333
2 weeks	5.0[ab]	5	3.3/7.8	4.0[b]	4	2.0/6.0	0.091	0.416
6 weeks	3.5[bc]	3	2.3/5.0	2.0[bc]	3	1.0/4.0	0.242	0.138
12 weeks	2.0[c]	2	1.0/3.0	2.0[c]	3	1.0/3.8	0.883	0.059
Difference (2 weeks-Baseline)	-2.0	2	-3.0/-1.0	-2.0	1	-3.0/-2.0	0.461	0.087
Difference (6 weeks-Baseline)	-4.5	3	-5.0/-3.0	-3.0	3	-5.0/-2.0	0.355	0.104
Difference (12 weeks-Baseline)	-5.0		-7.0/-4.0	-5.0	4	-5.8/-2.0	0.134	0.228
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			
Night								
Baseline	9.0[a]	1	9.0/10.0	8.5[a]	2	8.0/9.8	0.102	0.270
2 weeks	7.0[b]	5	4.0/8.8	5.0[ab]	4	3.0/7.0	0.134	0.341
6 weeks	4.0[bc]	3	2.0/5.0	3.0[bc]	4	1.3/5.5	0.445	0.083
12 weeks	2.5[c]	5	1.0/5.8	2.0[c]	4	1.0/5.0	0.718	0.078
Difference (2 weeks-Baseline)	-2.0	3	-3.8/-1.0	-2.0	4	-4.8/-1.3	0.547	0.107
Difference (6 weeks-Baseline)	-5.0	4	-7.0/-3.0	-5.0	5	6.8/-2.3	0.841	0.064
Difference (12 weeks-Baseline)	-7.0	5	-8.0/-3.0	-5.5	5	-7.8/-3.3	0.620	0.061
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			
Motion								
Baseline	10.0[a]	2	8.0/10.0	9.0[a]	2	8.0/10.0	0.165	0.207
2 weeks	6.0[ab]	3	5.0/8.0	6.0[b]	3	5.0/7.8	0.738	0.068
6 weeks	4.0[bc]	3	2.3/5.0	4.5[bc]	5	2.3/7.0	0.602	0.095
12 weeks	2.0[c]	5	0.3/5.0	2.0[c]	3	2.0/5.0	0.398	0.104
Difference (2 weeks-Baseline)	-5.0	3	-2.0/-1.3	-3.0	3	-2.0/-1.3	0.583	0.113
Difference (6 weeks-Baseline)	-5.0	3	-6.8/-4.0	-3.5	4	-6.0/-2.0	0.149	0.300
Difference (12 weeks-Baseline)	-6.0	5	-9.0/-4.3	-5.0	4	-7.0/-3.3	0.149	0.304
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			

VAS: Visual Analog Scale; PRP: platelet-rich plasma; IQR: Interquartile range; *p: Between group comparison using the Mann-Whitney U test; **p: Within group comparison using Friedman test followed by Nemenyi multiple comparison test. Significant *p* values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

RESULTS

Baseline characteristics of the PRP and control groups are summarized in Table 1. There were no significant differences in the age, sex, height, weight, body mass index, and involved arm between the groups (p>0.05). The median duration of symptoms was six (range, 3 to 8) years in the PRP group and three (range, 3 to 7) years in the control group, indicating no significant differences between the groups (p=0.812 and p=0.149, respectively).

However, there were significant differences in all status of VAS and SPADI scores for all time points after treatment compared to baseline in both groups (p<0.05). At the end of the study, there were no significant differences in all of VAS and SPADI scores between the PRP group and control group (p>0.05). In addition, there were significant differences in all status of active and passive ROM compared to baseline in both groups. A significant difference was observed in the active flexion, passive flexion, active abduction, passive abduction, and active external rotation scores at 12 weeks between the groups (p=0.012, p=0.015, p=0.008, p=0.019, and p=0.040, respectively), while no significant difference was noted between the groups in the other parameters (active and passive extension, active and passive internal rotation, passive external rotation) at 12 weeks (p=0.156, p=0.167, p=0.218, p=0.110, and p=0.081, respectively) (Table 2-10).

TABLE 5
Changes from baseline in the SPADI scores between PRP and control groups

	PRP group (n=20)			Control group (n=20)				
SPADI score	Median	IQR	25th-75th quartiles	Median	IQR	25th-75th quartiles	*p**	Post-power
Pain								
Baseline	92.0a	17.5	78.5/96.0	79.0[a]	19.0	72.5/91.5	0.121	0.128
2 weeks	68.0a	38.5	40.5/79.0	53.0[ab]	37.5	40.5/78.0	0.640	0.083
6 weeks	39.0b	33.0	20.5/53.5	40.0[bc]	25.5	26.0/51.5	0.841	0.101
12 weeks	21.0b	20.0	13.0/33.0	21.0[c]	23.8	12.0/35.7	0.968	0.050
Difference (2 weeks-Baseline)	-23.0	19	-31.0/-12.0	-20.0	23	-34.0/-10.5	0.968	0.051
Difference (6 weeks-Baseline)	-47.0	21	-56.0/-34.8	-40.0	36	-50.0/-26.0	0.242	0.252
Difference (12 weeks-Baseline)	-62.0	41	-76.0/-35.3	-57.0	25	-67.5/-40.8	0.495	0.079
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			
Disability								
Baseline	80.0[a]	26.9	71.5/88.4	72.5[a]	27.6	58.6/86.2	0.165	0.194
2 weeks	50.6[b]	39.9	33.9/73.8	47.5[b]	34.9	34.6/69.0	0.862	0.053
6 weeks	35.0[bc]	22.3	16.2/38.5	33.1[bc]	32.8	19.0/51.8	0.602	0.109
12 weeks	15.6[c]	28.8	0.0/28.7	18.7[c]	22.8	9.0/31.8	0.341	0.078
Difference (2 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.495	0.120
Difference (6 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.157	0.392
Difference (12 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.149	0.245
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			
Total								
Baseline	86.2[a]	15.2	78.6/93.8[a]	78.5[a]	20.9	69.0/90.0	0.121	0.137
2 weeks	60.4[a]	38.6	39.0/77.6[a]	55.0[b]	30.9	40.1/71.1	0.758	0.053
6 weeks	36.9[b]	30.2	17.3/47.4[b]	35.4[bc]	30.8	24.1/54.9	0.620	0.146
12 weeks	17.3[b]	30.0	7.1/37.1[b]	20.0[c]	23.8	10.1/34.0	0.620	0.061
Difference (2 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.583	0.087
Difference (6 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.183	0.373
Difference (12 weeks-Baseline)	-23.0	19	-31.0/-12.0	-23.0	19	-31.0/-12.0	0.142	0.137
*p***		**<0.001**			**<0.001**			
Post-power		1.000			1.000			

SPADI: Shoulder Pain and Disability Index; PRP: platelet-rich plasma; IQR: Interquartile range; *p: Between group comparison using the Mann-Whitney U test; **p: Within group comparison using Friedman test followed by Nemenyi multiple comparison test. Significant p values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

TABLE 6
Changes from baseline in the flexion scores between PRP and control groups

Flexion	PRP group (n=20) Mean±SD	Control group (n=20) Mean±SD	$p^{\star}$	Post-power
Active				
Baseline	94.0±28.5[a]	103.2±14.9[a]	0.208	0.239
2 weeks	126.0±31.3[b]	119.2±16.8[ab]	0.368	0.144
6 weeks	135.0±26.7[bc]	124.2±22.0[bc]	0.165	0.282
12 weeks	154.0±25.0[c]	134.0±23.0[c]	**0.012**	0.725
Difference (2 weeks–Baseline)	32.5±28.8	16.0±16.1	**0.031**	0.589
Difference (6 weeks–Baseline)	41.3±26.5	21.0±20.2	**0.010**	0.756
Difference (12 weeks–Baseline)	60.0±37.8	30.8±23.2	**0.005**	0.820
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		
Passive				
Baseline	106.2±27.6[a]	109.7±17.0[a]	0.633	0.076
2 weeks	134.5±32.6[ab]	127.0±18.5[ab]	0.378	0.140
6 weeks	145.0±24.0[bc]	132.0±21.9[bc]	0.082	0.413
12 weeks	161.5±22.7[c]	142.7±23.7[c]	**0.015**	0.701
Difference (2 weeks–Baseline)	28.3±20.5	17.3±16.9	0.072	0.438
Difference (6 weeks–Baseline)	38.8±17.2	22.3±19.5	**0.007**	0.789
Difference (12 weeks–Baseline)	55.3±32.8	33.0±24.1	**0.019**	0.664
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		

PRP: Platelet-rich plasma; SD: Standard deviation; p*: Between group comparison using the independent samples t test; p**: Within group comparison using one-way repeated measures analysis of variance followed by Bonferroni test. Significant *p* values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

TABLE 7
Changes from baseline in the extension scores between PRP and control groups

Extension	PRP group (n=20) Mean±SD	Control group (n=20) Mean±SD	$p^{\star}$	Post-power
Active				
Baseline	42.5±14.1[a]	43.7±9.0[a]	0.741	0.062
2 weeks	51.0±11.5[ab]	51.2±9.1[ab]	0.940	0.051
6 weeks	54.2±7.4[b]	52.7±10.0[b]	0.596	0.082
12 weeks	58.2±4.9[b]	55.0±8.7[b]	0.156	0.292
Difference (2 weeks–Baseline)	8.5±13.6	7.5±8.5	0.782	0.059
Difference (6 weeks–Baseline)	11.8±13.0	9.0±10.1	0.459	0.113
Difference (12 weeks–Baseline)	15.8±14.9	11.3±10.1	0.271	0.193
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		
Passive				
Baseline	45.5±8.2[a]	46.5±10.0[a]	0.732	0.063
2 weeks	54.0±9.8[b]	54.5±7.5[b]	0.858	0.054
6 weeks	56.7±4.9[b]	55.0±7.7[b]	0.401	0.132
12 weeks	59.5±1.5[b]	57.25±6.9[b]	0.167	0.279
Difference (2 weeks–Baseline)	8.5±8.1	8.0±9.2	0.857	0.054
Difference (6 weeks–Baseline)	11.3±7.0	8.5±10.5	0.338	0.157
Difference (12 weeks–Baseline)	14.0±8.0	10.8±10.2	0.269	0.194
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		

PRP: Platelet-rich plasma; SD: Standard deviation; p*: Between group comparison using the independent samples t test; p**: Within group comparison using one-way repeated measures analysis of variance followed by Bonferroni test. Significant p values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

TABLE 8
Changes from baseline in the abduction scores between PRP and control groups

	PRP group (n=20)	Control group (n=20)		
Abduction	Mean±SD	Mean±SD	p^*	Post-power
Active				
Baseline	77.7±20.6[a]	87.0±15.5[a]	0.118	0.345
2 weeks	114.0±35.6[b]	112.2±21.1[b]	0.851	0.054
6 weeks	123.2±32.0[bc]	110.5±26.9[b]	0.182	0.263
12 weeks	152.7±29.7[c]	126.2±30.3[b]	**0.008**	0.776
Difference (2 weeks–Baseline)	36.3±23.4	25.3±19.1	0.112	0.354
Difference (6 weeks–Baseline)	45.5±24.8	23.5±25.1	**0.008**	0.777
Difference (12 weeks–Baseline)	75.0±28.5	39.3±29.9	**<0.001**	0.965
p^{**}	**<0.001**	**<0.001**		
Post-power	1.000	1.000		
Passive				
Baseline	85.5±20.9[a]	94.5±19.5[a]	0.168	0.278
2 weeks	127.5±39.7[b]	120.0±23.3[b]	0.471	0.109
6 weeks	131.7±30.9[b]	119.5±29.1[b]	0.205	0.242
12 weeks	161.2±28.3[b]	138.2±31.0[b]	**0.019**	0.663
Difference (2 weeks–Baseline)	42.0±29.3	25.5±17.9	**0.039**	0.553
Difference (6 weeks–Baseline)	46.3±26.3	25.0±23.8	**0.011**	0.743
Difference (12 weeks–Baseline)	75.8±30.8	43.8±28.4	**0.002**	0.915
p^{**}	**<0.001**	**<0.001**		
Post-power	1.000	1.000		

PRP: Platelet-rich plasma; SD: Standard deviation; p*: Between group comparison using the independent samples t test; p**: Within group comparison using one-way repeated measures analysis of variance followed by Bonferroni test. Significant p values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

TABLE 9
Changes from baseline in the internal rotation scores between PRP and control groups

	PRP group (n=20)	Control group (n=20)		
Internal rotation	Mean±SD	Mean±SD	p^*	Post-power
Active				
Baseline	30.0±17.1[a]	35.0±15.7[a]	0.343	0.155
2 weeks	53.0±24.1[b]	56.7±19.2[b]	0.590	0.083
6 weeks	59.7±18.4b[c]	62.0±17.5[b]	0.695	0.067
12 weeks	73.7±11.3[c]	67.5±19.2[b]	0.218	0.231
Difference (2 weeks–Baseline)	23.3±24.4	21.8±20.7	0.862	0.053
Difference (6 weeks–Baseline)	29.8±19.0	27.0±19.0	0.650	0.073
Difference (12 weeks–Baseline)	43.8±19.4	32.5±20.9	0.086	0.405
p^{**}	**<0.001**	**<0.001**		
Post-power	1.000	1.000		
Passive				
Baseline	33.0±16.7[a]	37.5±16.3[a]	0.395	0.134
2 weeks	58.2±22.9[b]	60.5±17.3[b]	0.728	0.064
6 weeks	62.5±17.0[b]	65.2±15.7[b]	0.600	0.081
12 weeks	77.0±9.7[b]	69.7±17.2[b]	0.110	0.358
Difference (2 weeks–Baseline)	25.3±22.9	23.0±19.0	0.737	0.063
Difference (6 weeks–Baseline)	29.5±19.5	27.8±17.9	0.769	0.060
Difference (12 weeks–Baseline)	44.0±22.7	32.3±19.4	0.087	0.403
p^{**}	**<0.001**	**<0.001**		
Post-power	1.000	1.000		

PRP: Platelet-rich plasma; SD: Standard deviation; p*: Between group comparison using the independent samples t test; p**: Within group comparison using one-way repeated measures analysis of variance followed by Bonferroni test. Significant p values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

TABLE 10
Changes from baseline in the external rotation scores between PRP and control groups

	PRP group (n=20)	Control group (n=20)		
Internal rotation	Mean±SD	Mean±SD	$p^{\star}$	Post-power
Active				
Baseline	41.7±13.5[a]	46.7±13.7[a]	0.256	0.203
2 weeks	62.7±16.0[ab]	63.5±12.4[b]	0.870	0.053
6 weeks	71.2±14.4[bc]	66.5±13.5[bc]	0.292	0.181
12 weeks	82.2±13.6[c]	71.7±17.3[c]	**0.040**	0.546
Difference (2 weeks–Baseline)	21.0±17.4	16.8±12.4	0.378	0.140
Difference (6 weeks–Baseline)	29.5±17.5	19.8±14.2	0.060	0.472
Difference (12 weeks–Baseline)	40.5±19.5	25.0±15.5	**0.008**	0.776
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		
Passive				
Baseline	45.2±13.5[a]	50.2±14.8[a]	0.272	0.192
2 weeks	67.7±15.6[b]	67.5±12.9[b]	0.956	0.050
6 weeks	73.5±12.5[bc]	71.2±13.3[b]	0.587	0.083
12 weeks	83.7±12.4[c]	75.7±15.5[b]	0.081	0.416
Difference (2 weeks–Baseline)	22.5±15.2	17.3±12.4	0.238	0.215
Difference (6 weeks–Baseline)	28.3±15.9	21.0±15.0	0.147	0.304
Difference (12 weeks–Baseline)	38.5±17.3	25.5±16.5	**0.020**	0.658
$p^{\star\star}$	**<0.001**	**<0.001**		
Post-power	1.000	1.000		

PRP: Platelet-rich plasma; SD: Standard deviation; p*: Between group comparison using the independent samples t test; p**: Within group comparison using one-way repeated measures analysis of variance followed by Bonferroni test. Significant p values are shown in bold. Different superscripts in the same column indicate a statistically significant difference between time points.

DISCUSSION

In the present study, we attempted to investigate the effectiveness of PRP therapy in patients with adhesive capsulitis. To the best of our knowledge, this study is the first in the literature to contribute to the improvement in shoulder ROM scores, particularly in active flexion, passive flexion, active abduction, passive abduction, and active external rotation in patients with adhesive capsulitis with the addition of intra-articular PRP to the treatment of patients who exercise regularly. Of note, our study results demonstrated that PRP therapy could not make an additional contribution to exercise therapy in the scales of VAS and SPADI in these patients. Immediately after treatment at two weeks, both groups showed a significant improvement in all scores of all scales. Moreover, this healing process continued dramatically until the end of the study. This effect reaffirms the importance of exercise in the adhesive capsule with the synergy of PRP on ROM.

Review of the literature reveals a limited number of data regarding PRP applications in adhesive capsulitis. The effectiveness of PRP treatment in the adhesive capsule was first shown as a case in 2015.[20] In this case, Aslani et al.[20] applied PRP treatment seven months after the onset of symptoms. Stretching exercise was also recommended to the patient after each injection, and PRP was applied to the glenohumeral joint and the procedure was repeated after four weeks. Passive ROM by the goniometer, VAS, and Disability of Arm, Shoulder and Hand questionnaire was measured four weeks after the second application. Functional improvements of more than 70% based on the DASH questionnaire were observed. Moreover, healing outcomes were obtained in shoulder pain, flexion, abduction and external rotation. In our randomized-controlled study, the healing clinical results of the exercise and the combined PRP therapy were obtained, consistent with the aforementioned case.

Limitations in daily living activities due to pain and stiffness, impaired sleep quality due to nocturnal pain, fatigue, and depression can be seen in adhesive capsulitis.[21] In conservative treatment, several non-operative treatment modalities have been identified, including non-steroidal anti-inflammatory drugs, physical therapy, hydrodilatation, intra-articular steroid injection, and intra-articular hyaluronic acid injection.[21] Several complications such as fat atrophy, skin discoloration,

weakness, and thinning in ligaments and tendons can occur following intra-articular steroid injection.[22,23] If there is no response to these treatments, surgical treatment is indicated.

The exact cause of the lack of long-term effectiveness of intra-articular injection applications is still unclear, and alternative searches for the treatment are in progress. While the search for new treatments is ongoing, in a study by Barman et al.,[24] patients with adhesive capsulitis were divided into two groups and one group was given steroid and the other group PRP via intra-articular route. A total of 60 patients with adhesive capsulitis were assigned into two groups to receive 4 mL PRP and 4 mL corticosteroid via intra-articular injection. Both groups were given a routine home-based exercise program. The authors found that there were significant improvements in pain, disability, and ROM after 12 weeks in the PRP group. They also reported significant differences in all status of VAS and SPADI scores for all time points after treatment compared to baseline in both groups. In addition, these parameters were statistically significantly more improved over time in the PRP group compared to the corticosteroid group. On the other hand, Barman et al.[24] found significant increases in all ROM scores in both groups. In the inter-group comparison, statistically significant improvements were shown in the internal rotation, external rotation, active abduction and passive abduction in the PRP group. In our study, we did not use corticosteroids and we described exercise patients as the control group. We observed a greater improvement in terms of ROM scores, compared to the control group, while the VAS and SPADI scores were similar to the control group. The discrepancy in the efficacy results between the two studies may be related to the dose and preparation of PRP. Also, patients having a secondary etiology (such as diabetes) leading to adhesive capsulitis were not included in this study.

In another study of Lin,[25] the participants with adhesive capsulitis were divided into two groups as PRP and procaine, as a local anesthetic drug. The author found that the pain-point local injection with PRP was beneficial on the pain and the shoulder function, and the efficiency of PRP was also superior and longer than local procaine. To date, several studies have compared hyaluronic acid injection, steroid injection and physical therapy modality, and physical therapy modality was significantly superior to other modalities.[26,27] In our study, the healing effects of effective exercise therapy on pain and disability were shown to reach a very dramatic high degree.

The PRP promotes pro-inflammatory mechanisms by the growth factor, cytokines, and bioactive proteins in alpha granules of platelets and decreases inflammation. It provides repair and regeneration of injured articular cartilage and tissue repair.[28,29] In our study, positive results in joint movements obtained by adding PRP to exercise therapy may be associated with this mechanism.

Nonetheless, there are some limitations to this study. First, it could have been regulated with the placebo group receiving normal saline. However, we preferred applying exercise therapy studies with a longer follow-up period and including more patients as needed. Second, although the number of patients was sufficient to show the difference between time points in the groups, it was not enough to assess the difference between the groups according to the post-hoc power analysis. Nevertheless, while selecting patients with adhesive capsulitis, only patients with primary (idiopathic) etiology were included, and those with diabetes were, particularly, excluded. Indeed, this makes our study more valuable to observe the direct effectiveness of PRP.

In conclusion, home-based exercise therapy should be given more importance in patients with adhesive capsulitis. The addition of PRP to exercise treatment can improve patients' joint mobility, but not pain and disability in adhesive capsulitis. Further studies are needed to consider the effectiveness of PRP treatment in guidelines and to expand its administration in the clinical practice.

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