

# Comparison of ultrasound-guided platelet-rich plasma injection and conventional physical therapy for management of adhesive capsulitis: a randomized trial

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## Abstract

**Objective:** We evaluated the effect of ultrasound (US)-guided injection of platelet-rich plasma (PRP) into the shoulder joint in patients with adhesive capsulitis (AC) and compared its effect with that of conventional physiotherapy (CPT).

**Methods:** Sixty-four subjects with AC were included and randomly allocated into two groups, as follows: PRP (n=32; intra-articular [IA] PRP [4 mL] was injected); and CPT (n=32; short wave diathermy and exercise therapy were performed at three sessions/week for 6 weeks). Treatment outcomes evaluated therapeutic effectiveness before and at 1, 3, and 6 weeks after PRP injection and CPT initiation.

**Results:** Subjects in both groups showed a significant decrease in the visual analogue scale score for pain and shoulder and hand scores, and they a significant increase in shoulder passive range of motion at all evaluation time points. There was no significant difference in the measured outcomes between the two groups. However, there was less acetaminophen consumption after IA PRP injection compared with that after CPT.

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**Conclusions:** IA PRP injection is a useful option for treating patients with AC, particularly those who have low therapeutic compliance for exercise therapy or have contraindications for corticosteroid injection or oral pain reduction medication.

### Keywords

Shoulder, platelet-rich plasma, pain, pain management, range of motion, articular, ultrasonography

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## Introduction

Adhesive capsulitis (AC) of the shoulder is a common clinical condition that is characterized by insidious and progressive pain and loss of active and passive range of motion (ROM) in the glenohumeral (GH) joint, and it is associated with significant morbidity.<sup>1,2</sup> AC affects 2% to 5% of the general population and 10% to 38% of patients with diabetes and thyroid disease.<sup>2,3</sup> Its peak incidence is in people between 40 and 60 years of age, and it is slightly more common in women.<sup>2,3</sup>

The etiology of AC remains unclear. It has been postulated that a minor insult could initiate an inflammatory healing response, which may lead to excess accumulation and propagation of fibroblasts that release type I and type III collagen. This, in turn, results in an imbalance between fibrosis and a loss of normal collagenous remodeling, which leads to limitations of the shoulder joint.<sup>4,5</sup>

The definitive treatment to manage AC of the shoulder joint remains uncertain. Recently, many clinicians have administered corticosteroid injections to manage AC symptoms.<sup>6</sup> However, these may cause clinical complications such as increased probability of tendon rupture, post-injection pain, subcutaneous atrophy, and skin depigmentation.<sup>7,8</sup> Moreover, oral medications for pain reduction have several

side effects, such as gastrointestinal, renal, and vascular problems.

A new treatment is an injection of platelet-rich plasma (PRP), which is a blood derivative that has a higher platelet concentration than whole blood, and it contains growth factors that stimulate cellular anabolism and modulators that exert anti-inflammatory and analgesic effects.<sup>9–12</sup> Because the inflammatory process and fibrosis in the synovium are responsible for the development of AC, direct injection of PRP into the GH joint may effectively manage pain and stiffness of the shoulder joint in AC.<sup>12,13</sup> However, little is known about the effectiveness of ultrasound (US)-guided intra-articular (IA) PRP injection for treating AC.

In our study, we explored the effectiveness of US-guided injection of PRP into the shoulder joint of patients with AC. We also compared its effect with that of conventional physiotherapy (CPT).

## Materials and methods

### *Ethics approval and consent to participate*

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Institutional Review Board Ethics Committee of a university hospital

(number: 98 (Rehab)/UMM/2017). Written informed consent was obtained from each patient.

### Subjects

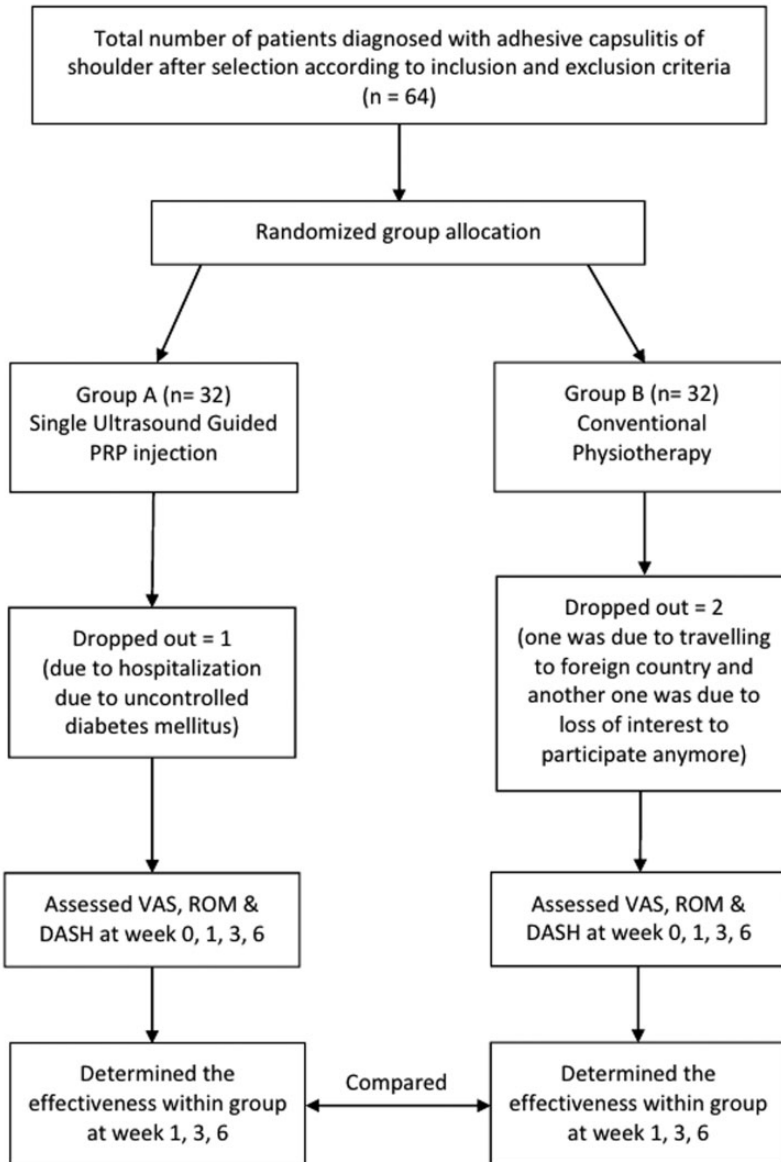
We evaluated patients who presented with shoulder pain and motion limitation in the shoulder joint. Sixty-four consecutive patients who visited an outpatient pain clinic were included on the basis of the following inclusion criteria: (1) pain onset <3 months ago; (2) shoulder pain aggravation when moving the shoulder joint; (3) significant limitations of passive shoulder motion in more than one plane of the shoulder; (4) age 20 to 65 years; and (5) visual analog scale (VAS) score for pain  $\geq 50$ . The exclusion criteria were as follows: (1) bilateral AC of the shoulder; (2) previous GH joint injection within 6 months; (3) history of shoulder joint dislocation or previous shoulder surgery; and (4) contraindications to the injection procedure such as local cellulitis, septic arthritis, and acute fracture. The Institutional Review Board of a university hospital approved the study (number: 98 (Rehab)/UMM/2017), and all the patients signed an informed consent form.

We calculated the sample size based on a previous study,<sup>14</sup> in which the mean differences in the VAS score for pain after PRP injections and CPT were 13.0 and 16.6, respectively. Therefore, the mean difference in the VAS score change after the two treatments was 3.6. When we used a type I error of 0.05, a power of 80%, and a two-sided test, 28 subjects per group were required for our study. Using 10% as the dropout rate, we needed to recruit 32 subjects in each group. Sixty-four patients with AC were randomly assigned to one of the two study groups. Randomization was performed using a random number table. Thirty-two patients were included in the US-guided IA PRP injection group (PRP group) and 32 in the CPT group. Patients who did not

attend regular CPT session for 2 consecutive weeks were considered to be drop-outs (Figure 1).

### Procedures

Patients in the PRP group received US (SonixOP, Burnaby, Canada)-guided autologous PRP injection into the GH joint. We used a 13- to 6-MHz linear array transducer. A single injection was performed during the study period. The patient's blood was drawn using a 10-mL syringe. It was then transferred into a PRP tube (Manson, Beijing, China; power PRP tube, triple sterilization process) containing acid citrate dextrose (ACD) as an anticoagulant, calcium chloride ( $\text{CaCl}_2$ ) for platelet activation, and separation gel between the red blood cells (RBCs) and plasma. The samples were then centrifuged at  $1500 \times g$  for 8 minutes, as recommended by the manufacturer. Samples from the lower portion of the PRP tube were removed to obtain 4 mL of PRP. The patient sat in an upright position, and the physiatrist (ACT) who performed the injection stood behind the patient. The hand of the arm for which the GH was being injected (ipsilateral hand) was positioned on the patient's contralateral shoulder. The US transducer was positioned over the long axis of the myotendinous junction of the infraspinatus tendon to view the contours of the posterior glenoid rim, the posterior glenoid labrum, and the posterior portion of the humeral head. The needle was advanced using real-time US equipment until the needle tip entered the GH joint. Then, 4 mL of PRP mixed with 1 mL of 2% lidocaine was injected into the GH joint using a 22-gauge spinal needle under aseptic conditions, which was parallel to the US probe in a semioblique plane until the tip of the needle entered the GH joint.<sup>6</sup> After the injection, specific CPT was not conducted.



**Figure 1.** CONSORT diagram

Patients in the CPT group received short wave diathermy (SWD) (27.12 MHz) for 15 minutes and exercise therapy for 30 minutes (stretching exercises within their pain limit, active and passive ROM exercises, and pulley exercises). CPT was conducted in three sessions per week for 6 weeks.

### *Outcome measures*

The same investigator measured the treatment outcomes before the treatment and at 1, 3, and 6 weeks after PRP injection or CPT initiation. The investigator was blinded to the patient grouping and did

not participate in any treatment. Pain was evaluated using a VAS, and the shoulder joint's passive ROM (flexion, abduction, and external rotation) was measured using a hand-held goniometer in the supine position. The passive shoulder ROM was measured by moving the subject's arm until it was limited mechanically. Functional assessment was performed using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire. The DASH is a valid and responsive questionnaire that is used to evaluate disability in patients with shoulder, arm, and hand complaints. The DASH score ranged from 0 to 100, with higher scores indicating greater disability. One investigator, who was blinded to group allocation and did not participate in any treatment, measured all outcomes. Additionally, patients were allowed to take acetaminophen (650 mg) for intolerable pain once a day during the study period. We investigated the number of patients who were taking acetaminophen per day.

### *Statistical analysis*

Data were analyzed using the Statistical Package for Social Science (SPSS, v. 25.0, IBM Corp., Armonk, NY, USA). The Chi-square test and the Mann–Whitney U-test were used to compare the demographic data and the number of patients taking acetaminophen between the two groups. Within each group, changes in the measured outcomes were evaluated using repeated-measure one-factor analysis. To compare the clinical changes over time between groups, repeated two-factor analysis was used. Multiple comparison results were obtained following an adjustment using the Bonferroni correction. The level of statistical significance was set at  $p < 0.05$ .

## **Results**

### *Patients' clinical characteristics*

Sixty-four patients with AC were randomized into either of the following two study groups: IA PRP ( $n=32$ ) or CPT ( $n=32$ ). During the study period, three participants dropped out (one from the PRP group because of hospitalization for uncontrolled diabetes mellitus and two from the CPT group because of foreign country travel and loss of interest in participation in this study). Thus, there were 61 (95%) patients who completed the program (31 in the IA PRP group and 30 in the CPT group). In both groups, there were no severe side effects. In the IA PRP group, the average was  $52.84 \pm 6.92$  years, while that in the CPT group was  $57.17 \pm 6.93$ . In the IA PRP group, there were 27 women and four men, and in the CPT group, there were 21 women and nine men. Table 1 shows the demographic and initial clinical characteristics of the study subjects. Significant differences were not found between the two groups for all parameters except age, which was significantly higher in the CPT group compared with the IA PRP group ( $p=0.018$ ).

### *Changes in VAS, DASH, and ROM*

After the IA PRP injection, five patients had pain of non-severe intensity. To control the post-injection pain, we prescribed acetaminophen (650 mg). Pain in the shoulder joint (indicated by the VAS score) and function of the upper limb (indicated by the DASH score) were significantly lower at 1, 3, and 6 weeks after IA PRP injection and CPT compared with the scores before the treatments ( $p < 0.001$ ) (Table 2). However, the changes in VAS and DASH scores over time were not significantly different at 1, 3, and 6 weeks after each treatment between the two groups (Table 2).

**Table 1.** Demographic and baseline clinical data in the PRP and CPT groups

Variable	IA PRP (n=31)	CPT (n=30)	p-value
Age (years)	52.84±6.92 / 51 (10)	57.17±6.93 / 59 (14)	0.018†
Sex			
Male	4 (12.9)	9 (30.0)	N.S.§
Female	27 (87.1)	21 (70.0)	
Affected side			
Right	17 (54.8)	21 (70.0)	N.S.§
Left	14 (45.2)	9 (30.0)	
DM	3 (9.7)	4 (13.3)	N.S.§
VAS (mm)	82.9±14.42 / 90 (20)	82.67±14.37 / 80 (30)	N.S.‡
DASH	52.9±14.18 / 52.2 (22.5)	53.81±10.72 / 57 (16.8)	N.S.‡
ROM (Degree)			
Flexion	104.84±15.89 / 110 (30)	101.83±16.43 / 95 (26.3)	N.S.‡
Abduction	93.23±22.86 / 90 (30)	90.17±23.73 / 90 (32.5)	N.S.‡
External rotation	56.45±15.5 / 55 (20)	52.67±16.6 / 52.5 (26.3)	N.S.‡

Values are presented as the mean±standard deviation /median (interquartile range) or frequency (percent).

§: Result by the chi-square test.

†: Result by the two-sample t-test with normality assumption.

‡: Result by the Mann–Whitney U-test without normality assumption.

PRP, platelet-rich plasma; CPT, conventional physiotherapy; IA, intra-articular; DM, diabetes mellitus; VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand; ROM, range of motion; N.S., not significant.

For passive shoulder ROM at the 1-, 3-, and 6-week follow-ups, the ROMs (flexion, abduction, external rotation) were significantly improved compared with those at the initial evaluation in both groups ( $p < 0.001$ ; Table 2). However, the changes in ROMs over time at the 1-, 3-, and 6-week follow-up visits were not significantly different between the two groups (Table 2).

### Number of patients taking acetaminophen

The number of patients taking acetaminophen during 0 to 1 week, 1 to 3 weeks, and 3 to 6 weeks after IA PRP injection and CPT was significantly lower in the PRP group compared with the CPT group ( $p = 0.005$ ,  $0.005$ , and  $0.002$ , respectively; Table 3).

## Discussion

In the present study, we compared the effectiveness of IA PRP injection and CPT to

treat patients with AC. After receiving the US-guided IA PRP injection, shoulder joint pain was reduced significantly compared with that at baseline. Similarly, CPT also significantly reduced pain compared with baseline. The function of the upper limb and passive ROM of the shoulder joint were significantly improved after each treatment. The effect of IA PRP injection was sustained for at least 6 weeks. There was no significant difference in terms of pain, function of the upper limb, or passive ROM degree between the two groups. However, the number of patients taking acetaminophen was significantly lower in the PRP group than in the CPT group.

Some possible mechanisms have been proposed for the action of PRP.<sup>12,13,15,16</sup> The main mechanism of action of PRP is through platelets. Platelets function as a natural reservoir for growth factors, and they play an essential role in tissue healing and regeneration. Various growth factors that are released from platelets promote

**Table 2.** Changes in the VAS, DASH, and ROM of the shoulder joint

Variable	Group	Pre-treatment (p)	1 week (1)	3 weeks (3)	6 weeks (6)	p-value†		p-value‡	
						p < 1 < 3 < 6 §	T	G	T*G
VAS	CPT group	52.67 ± 16.60	64.33 ± 14.19	71.67 ± 12.89	78.83 ± 9.16	<.001	p < 1 < 3 < 6 §	T	G
	PRP group	82.90 ± 14.42	59.35 ± 15.48	45.16 ± 16.91	28.39 ± 14.63	<.001	p > 1 > 3 > 6 §	<.001	N.S.
	CPT group	82.67 ± 14.37	63.00 ± 13.17	49.67 ± 15.20	31.00 ± 14.94	<.001	p > 1 > 3 > 6 §	p > 1 > 3 > 6 §	N.S.
DASH	PRP group	52.90 ± 14.18	37.48 ± 13.93	24.92 ± 13.82	14.35 ± 10.74	<.001	p > 1 > 3 > 6 §	<.001	N.S.
	CPT group	53.81 ± 10.72	40.83 ± 12.24	29.86 ± 12.82	19.55 ± 12.47	<.001	p > 1 > 3 > 6 §	p > 1 > 3 > 6 §	N.S.
ROM-Flexion	PRP group	104.84 ± 15.89	118.87 ± 14.18	133.39 ± 15.83	146.45 ± 12.92	<.001	p < 1 < 3 < 6 §	<.001	N.S.
	CPT group	101.83 ± 16.43	115.67 ± 14.06	131.17 ± 14.06	142.17 ± 12.30	<.001	p < 1 < 3 < 6 §	p < 1 < 3 < 6 §	N.S.
ROM-Abduction	PRP group	93.23 ± 22.86	110.65 ± 21.01	124.84 ± 21.62	132.10 ± 19.44	<.001	p < 1 < 3 < 6 §	<.001	N.S.
	CPT group	90.17 ± 23.73	108.67 ± 19.16	121.17 ± 16.54	130.17 ± 17.29	<.001	p < 1 < 3 < 6 §	p < 1 < 3 < 6 §	N.S.
ROM-External rotation	PRP group	56.45 ± 15.50	67.58 ± 15.59	73.87 ± 14.65	80.81 ± 11.26	<.001	p < 1 < 3 < 6 §	<.001	N.S.
	CPT group	52.67 ± 16.60	64.33 ± 14.19	71.67 ± 12.89	78.83 ± 9.16	<.001	p < 1 < 3 < 6 §	p < 1 < 3 < 6 §	N.S.

Values are presented as the mean ± standard deviation.

†: Result by repeated measures one-factor analysis.

‡: Result by repeated measure two-factor analysis.

§: Multiple comparison result by contrast.

In the intragroup comparison, the VAS and DASH scores and shoulder flexion showed a significant decrease after intra-articular platelet-rich plasma (PRP) injection and initiation of conventional physiotherapy (CPT). Abduction and external rotation ROM scores showed a significant increase. However, in the intergroup comparison, changes on the basis of time for these outcomes were not significantly different between the two groups (PRP group, 31 patients; CPT group, 30 patients).

PRP, platelet-rich plasma; CPT, conventional physiotherapy; VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand; ROM, range of motion; T, time; G, group; N.S., not significant.

**Table 3.** Number of patients taking acetaminophen in the PRP (n=31) and CPT (n=30) groups

	IA PRP (n=31)	CPT (n=30)	p-value
0–1 week	11.9±5.04 / 12 (7)	15.7±6.55 / 15.5 (8)	0.005‡
1–3 weeks	7.45±5.55 / 7 (12)	11.53±5.78 / 14 (7.3)	0.005‡
3–6 weeks	2.68±4.04 / 0 (4)	7.7±6.31 / 7.5 (14)	0.002‡

The number of patients taking acetaminophen per day is presented as the mean±standard deviation / median (interquartile range) during weeks 0 to 1, 1 to 3, and 3 to 6 after the PRP injection or the initiation of CPT.

‡: Result by the Mann–Whitney U-test without a normality assumption.

PRP, platelet-rich plasma; CPT, conventional physiotherapy; IA, intra-articular.

angiogenesis and tissue repair.<sup>12,13,15,16</sup> These growth factors also stimulate the healing process by attracting cells to the newly formed matrix and triggering cell division. This, in turn, can reduce synovial membrane hyperplasia. Additionally, PRP can exert an anti-inflammatory effect at the inflammation site by releasing cytokines and recruiting leukocytes.<sup>12,13</sup> Platelets release tumor necrosis factor- $\alpha$  and hepatocyte growth factor, which are potent anti-inflammatory agents.<sup>17</sup> Moreover, they promote the secretion of lipoxin A<sub>4</sub>, which has anti-inflammatory properties.<sup>18</sup> Therefore, PRP may affect all the phases of tissue healing in AC (i.e., inflammatory, proliferative, and remodeling phases), which may result in pain reduction and improvement of shoulder function and ROM in patients with AC.<sup>13</sup> However, the aforementioned mechanisms in the joint space of AC patients were not clearly demonstrated. We did not evaluate the molecular basis of PRP action on the joint structure. Moreover, further studies are needed to confirm the mechanisms of PRP in reducing shoulder pain and increasing the ROM in patients with AC.

CPT is an effective treatment for AC. Several previous studies have demonstrated that stretching or strengthening exercises of the shoulder reduce pain and increase shoulder joint function.<sup>19–21</sup> Tiwari et al.<sup>22</sup> reported that SWD decreases the tensile stress in soft tissues, which leads to a

decrease in pain and an increase in the mobility of the shoulder joint. Leung et al.<sup>23</sup> reported that SWD plus stretching exercises significantly increase the shoulder score index compared with stretching alone in patients with AC. However, when using CPT to treat AC, CPT should be conducted regularly and frequently; therefore, a lot of time is required for the treatment, and the treatment compliance with CPT might be poor. In our study, CPT and PRP injection had similar effects on pain reduction and improvement in the shoulder joint function. Additionally, patients who underwent PRP therapy consumed less acetaminophen compared with patients who underwent CPT. However, we cannot rule out that 1 mL of 2% lidocaine and PRP contributed to the lower use of acetaminophen in the PRP group. We believe that IA PRP injection can be a good independent treatment alternative or that it can be used in conjunction with CPT for AC.

For the effect of IA PRP injection on patients with AC, only three studies have been reported to date.<sup>13,24,25</sup> In 2018, Lin<sup>25</sup> recruited 60 patients with AC, and randomly divided them into two groups (30 patients who received IA PRP injection and 30 patients who received IA procaine injection). Stretching and strengthening exercises were performed in both groups for 6 weeks after each procedure. They found that both the treatments were effective, but PRP injection was more effective



and had a more prolonged efficiency of pain reduction and functional improvement than procaine injection. In 2019, Barman et al.<sup>13</sup> performed IA PRP injection in patients with AC (30 patients) and compared its effect on pain reduction, functional improvement, and ROM increment with IA corticosteroid injection (30 patients). At 12 weeks after each procedure, the effect was greater in patients who received IA PRP injection. In 2020, Bölük Şenlikci<sup>24</sup> injected IA PRP into the shoulder joint of a patient with chronic kidney disease, and they found that the symptoms of AC could be successfully managed. The authors suggested that IA PRP injection is a good treatment option for patients with AC who have contraindications for corticosteroid injection or oral medication for pain reduction. Our study is the first to compare the effect of IA PRP injection with that of CPT in patients with AC.

The appropriate number of IA PRP injections was not evaluated. However, in several previous studies,<sup>13,25,26</sup> a single IA PRP injection successfully alleviated the symptoms of AC, which is consistent with the results of our study. Therefore, we suggest that a single IA PRP injection without repeated injections would be a sufficient treatment for patients with AC.

The most appropriate site for a PRP injection to treat AC has not been established. Previous studies confirmed that inflammatory factors are mainly concentrated in the GH joint cavity in AC.<sup>27-29</sup> On the basis of these results, Oh et al.'s<sup>30</sup> study suggested that an intraarticular injection may have a better effect on pain relief than a subacromial injection in the treatment of AC. Therefore, we injected PRP into the GH joint, which can directly target the inflammatory factors.

To measure the shoulder ROM, Cyriax et al.<sup>31</sup> described that reductions of the anterior joint capsule space and inferior redundant joint capsular fold are prominent

in AC, which cause limitations of shoulder abduction and external rotation. However, the relatively posterior joint capsule space is less reduced in AC. Thus, internal rotation in patients with AC is less affected, and we did not evaluate internal rotation ROM in our study.

In this study, no major adverse effects were observed in either group. In the PRP group, five patients had post-injection pain of non-severe intensity. Several previous studies<sup>13,25,26</sup> also reported mild to moderate pain at the injection sites after a PRP injection, but no serious adverse events, such as infection or systemic symptoms, were reported. Therefore, IA PRP may be safe for managing symptoms of AC.

In conclusion, we found that US-guided IA PRP injection into the shoulder joint of patients with AC had a comparable effect on pain reduction, functional improvement, and shoulder joint ROM increment compared with regular CPT. Less acetaminophen was consumed after IA PRP injection compared with CPT. Thus, IA PRP injection can be a useful treatment method for AC, particularly in patients who have low therapeutic compliance or have contraindications to corticosteroid injection or oral medication for pain reduction. Our study is limited because there was a relatively short follow-up period and a small sample size. Further studies that address these limitations are warranted.

#### **Availability of data and materials**

All data included in this study are available upon request by contact with the corresponding author.

#### **Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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## Authors' contributions

ACT, WNS, LMH, and TTHH performed the experiments and collected the results. All authors wrote the manuscript. ACT, SGK, and MCC contributed to data analysis and manuscript revision. All authors conceived the study and contributed to reviewing/editing the manuscript. All authors read and approved the final manuscript.

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