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The role of platelet-rich plasma in shoulder pathologies: a critical review of the literature

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- Platelet-rich plasma (PRP) is a revolutionary treatment that harnesses the regenerative power of the body's own platelets to promote healing and tissue regeneration.
- While PRP therapy has emerged as a promising option for augmenting biologic healing in the shoulder, the complexity of shoulder disorders makes it difficult to draw definitive conclusions about the efficacy of PRP across different conditions and stages of disease.
- Our comprehensive review of twenty-four studies highlights the current state of PRP therapy in shoulder pathologies, revealing a wide variety of number of patients, control groups and results. Despite these challenges, the regenerative potential of PRP therapy is moderate in some conditions, with numerous studies demonstrating the positive effects.
- In conclusion, the authors of this study recommend the use of PRP therapy for adhesive capsulitis and rotator cuff repair of medium to large tears. However, they do not recommend the use of PRP for subacromial impingement or rotator cuff tears. It is up to the clinician's discretion to decide whether PRP therapy is appropriate for individual cases. However, there is still insufficient evidence to support the inclusion of PRP therapy in treatment protocols for other shoulder disorders. Therefore, further research is needed to fully explore the potential of PRP therapy in the treatment of various shoulder conditions.

Keywords

- Platelet-rich plasma (PRP)
- shoulder pathologies
- review

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Introduction

Platelet-rich plasma (PRP) is a platelet concentrate (PC) derived from autologous blood which contains a three to ten times higher concentration of platelets than normal peripheral blood (150 000–350 000 platelets/μL) (1, 2, 3). Additionally, it contains the full complement of cytokines, clotting and growth factors necessary for tissue and wound healing when an individual has sustained an injury (4, 5). Originally used in 1970 to treat patients with thrombocytopenia, subsequent years have seen its application extended to the fields of dermatology, oral maxillofacial, craniofacial, plastic surgery, neurosurgery and orthopedics, with the hope of aiding biological repair processes in difficult-to-treat soft tissue pathologic processes (6).

In orthopedics, PRP has been reported to have value in the treatment of several disorders involving cartilage, muscles, tendons, ligaments and plica. Nevertheless, evidence remains contradictory, and high-quality clinical trials with long-term follow-up are needed to elucidate PRP's real value in specific disease processes (7, 8). For example, PRP has been shown to play a role in tendon healing through both cellular and humeral mediators (9), and its use in tendinopathy has shown some promise clinically for lateral epicondyle tendinopathy (10). As an augmentation during surgical intervention, PRP has been studied in rotator cuff repair, anterior cruciate ligament surgery and Achilles tendon repair and has also been studied with limited evidence for efficacy due to controversial reports and inconclusive evidence (11, 12). In contrast, in ankle sprains and muscle injuries, PRP

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had the same efficacy when compared to placebo, thus lacking its benefits of application (13, 14). Despite studies with conflicting evidence for PRP's efficacy, and perhaps because of its safety, it continues to be studied and used extensively. In a recent study by Zhang *et al.* in the USA, PRP was most commonly used in the treatment of knee meniscal and plica disorders, followed by unspecified shoulder conditions, rotator cuff injuries, epicondylopathy and plantar fasciitis (15). Nevertheless, while the results in lateral epicondyle tendinopathy have been encouraging, and the explosion of its use in other soft tissue disorders continues to grow, there remains significant controversy in treatment efficacy as to whether outcomes change with the type of PRP formulation, delivery method, stage of disease and whether positive results extend to other anatomic locations (16, 17).

Because of the ever-growing and changing landscape of PRP formulation and efficacy reports, clinicians have difficulty knowing which formulation and delivery method to select, for whom and for what anatomic location and pathology. In the shoulder, the burden of disease continues to rise. Therefore, strategies to augment biologic healing remain attractive. Nevertheless, the literature in support of PRP is difficult to interpret for different disorders, chronicity and stage of the disorder in the shoulder. Therefore, we aim to critically review the efficacy of PRP in shoulder disorders with a special focus on its use in the treatment of rotator cuff disorders.

Preparation, classification and application

There are a plethora of different protocols for PRP preparation with no consensus on optimal component concentrations, including the concentration of platelets, growth factors and leukocytes within these formulations (15). This variability has resulted in great difficulty in our ability to compare different studies on the role, efficacy, advantages and disadvantages of PRP. Nevertheless, all methods aim to increase the platelet concentration through a process known as differential centrifugation, to achieve a 'therapeutic' platelet concentration. A variety of PRP preparations are due to a wide range of the number of centrifugation cycles, force of centrifugation and even the types of centrifuges utilized in preparation. Despite this variability, simple centrifugation has generally been recommended for the day-to-day use of PRP in surgery (18).

In general, there are two methods of PRP preparation (19):

1. Plasma layer method
    a. Two phases of centrifugation are used: In the first phase, red blood cells (RBCs) are separated followed by a second phase in which, platelets are concentrated. PRP is created from the pellets in the lower one-third of plasma layer.
2. Buffy method
    a. In this method, the whole blood is centrifuged at a 'high speed' with subsequent collection of the buffy coat. The buffy coat contains a high concentration of leukocytes.

Regarding the devices used, there are two different methods of obtaining blood for PRP preparations. In the open technique, instruments, collection tubes and pipettes are exposed to the environment of the working area. In contrast, the closed technique utilizes different commercial devices to obtain and prepare the product without exposure to the ambient environment. Due to sterility, variability and quality control issues, the closed method is generally preferred over the open (20).

There are many classifications regarding PC formulation, but one of the best characterized and utilized schemes was proposed by Ehrenfest *et al.* who defined four main categories (21):

1. Leukocyte-poor or pure platelet-rich plasma (PRP)
    a. Usually 40 mL of PC is obtained from 450 mL of whole blood and produces pure platelet concentrate with small amounts of residual RBCs and leukocytes remaining.
2. Leukocyte- and platelet-rich plasma (L-PRP)
    a. The PRP concentrate obtained with this method is composed of a high quantity of platelets, leukocytes and circulating fibrinogen and small amounts of residual RBCs.
3. Leukocyte-poor or pure platelet-rich fibrin (P-PRF)
    a. Whole blood is mixed with anticoagulant and a separation gel, leading to a platelet-rich fibrin scaffold.
4. Leukocyte- and platelet-rich fibrin (L-PRF)
    a. Produced with a simple technique, called Choukroun's PRF protocol, a natural concentrate is produced in the absence of anticoagulant agents. This formulation clots and is delivered locally in plastic and maxillofacial surgery.

Despite an intuitive sense that 'more is better', this is not supported in the literature, and a higher concentration of platelets does not necessarily translate into greater efficacy (22). This may be due to inconsistencies between platelet count and growth factor concentration both by preparation type, including leukocyte-poor or leucocyte-rich PRP, and between individuals. White blood cells produce growth factors under specific conditions, and varying the concentration of these cells alters the final growth factor concentration in PRP (23). Further, premature platelet activation decreases the concentration of growth factors when discarding the supernatant for certain preparations of PRP.

PRP in rotator cuff diseases

PRP in rotator cuff tears

PRP is one of the most common biologic treatment therapies for rotator cuff tears and tendinopathies (24). Two randomized controlled trials (RCTs) (25, 26) compared PRP to saline in injections to the subacromial space for partial tears and tendinopathies. The first trial examined 40 patients with partial tears or tendinopathy. At 1-year follow-up, these authors found no benefits of L-PRP injections to the quality of life, pain, disability and shoulder range of motion (ROM) (25). The second study examined 80 adults with symptomatic isolated interstitial tears of the supraspinatus. The authors of this study used two injections separated by 1 month of either the placebo (saline) or P-PRP. Primary outcomes were clinical scores and tendon healing measures. Similar to the first study, at a minimum of 1-year follow-up, P-PRP neither improved clinical scores or tendon healing. Concerningly, it was also associated with more adverse events (26).

In contrast to these studies, PRP has shown some benefits in partial tears and tendinopathy when compared to corticosteroids (CSs) in the short term (27, 28). In a level 1 study by Kwong *et al.*, P-PRP had superior functional outcomes over CS in the short term (3 months) in 99 patients with partial rotator cuff tears. Nevertheless, the long-term benefit (12 months) was similar between groups (28). In another level 1 study with 58 patients and rotator cuff tendinitis or partial rotator cuff tears, no benefit was found for L-PRP over CS at 3 months in functional scores, but pain and ROM did significantly improve. These authors suggest the use of L-PRP when there is a contraindication to CS injections (29).

In a level 2 study comparing P-PRP vs CS in the treatment of 40 patients with symptomatic partial rotator cuff tears, the authors found P-PRP had better early clinical outcomes compared to CS, but the results were not sustained after 6 months. These authors also recommended P-PRP *in lieu* of CS in patients with partial rotator cuff tears and concomitant contraindication to CS (30). In a level 3 therapeutic study of 50 patients with symptomatic rotator cuff tears, the authors compared three sequential injections of P-PRP separated by 7-day intervals to CS. Similar to those previously reported, this study found P-PRP had greater benefits compared to CS early on but no statistically significant differences after 6 months (31).

As previously alluded to, the contradictory results from different studies might be explained by the variability of the application, the frequency of the PRP and possibly postintervention programs. For example in the Kwong study, P-PRP injections were divided between the site of tendon pathology and the subacromial space (28), while in the Dadgostar *et al.* study, L-PRP was divided between the tendon pathology and the intra-articular space (29). In contrast, Kesikburun *et al.* infiltrated the L-PRP only into the lesion, dividing the preparation between the center and four sites around the lesion (25), while two other studies applied the full dose of P-PRP into the subacromial space (30, 31). While some studies applied a single dose of PRP (25, 28, 29, 30), others utilized several injections (26, 31). Finally, regarding postinterventional regimens, most prohibited the use of NSAIDs (non-steroidal anti-inflammatory drugs) for a 6-month period and some protocols allowed home exercise (28, 29, 30) or physical therapy (25), while in others, only passive movement was advised (26, 31).

Despite the methodological differences of the abovementioned studies, there remains one consistent finding – positive results at 3 months in the PRP-treated groups. Nevertheless, these results do not persist for 1 year, and no benefit in any clinical or healing outcome was observed at this time point. Therefore, the value of PRP is still open to the debate depending on the goal of treatment – early vs late treatment effect and the alternatives to treatment (the ability of the patient to participate in physiotherapy or have a CS injection).

Based on the current literature, even P-PRPs did not lead to a better clinical outcome at the 6 and 12 month follow-up and can therefore not be recommended. Please see Table 1 for more details.

PRP augmentation in rotator cuff tear repairs

Rotator cuff tears can be successfully treated with arthroscopic repair after failure of conservative treatment (32, 33). Unfortunately, retear rates remain one of the most common complications of this procedure ranging from 11% to 57% (34, 35, 36, 37, 38). Furthermore, no single preoperative or intraoperative factor has been shown to predict retear risk (39). PRP has been promoted as an additional biologic adjunct after rotator cuff repair to strengthen repairs and lower retear risks (40, 41, 42).

The use of PRP after repair of small-to-medium rotator cuff tear has been shown not to be cost-effective (42), and another study also found that PRP is not cost-effective after full-thickness rotator cuff tear without determining the size of the tear (43). However, there is a great variability of the price of PRP in different countries, while in the USA the cost of 1 PRP injection is $714 (44) and the price in Japan is around $195 (45).

Jo *et al.* published two RCTs comparing the efficacy of P-PRP augmentation to surgery alone after arthroscopic repair of rotator cuff tears (46, 47). In both studies, the authors used their own technique to prepare a P-PRP gel for augmentation at the time of surgery (48). In the first study, 74 patients with medium-to-large rotator cuff tears were augmented. The authors found that while functional results were the same, supraspinatus quality was significantly greater in the P-PRP group and retear

Table 1 Effectiveness of P-PRP and L-PRPin rotator cuff tears.

Study	Study design	Patients enrolled				Outcome	Use of PRP
		Total	PRP	CS	Saline		
Kwong *et al.* (28)	RCT	99	47	52		P-PRP was superior in pain and function at 3 mo FU. No benefit of P-PRP over CS at 12 months FU	+ (P-PRP)
Dadgostar *et al.* (29)	RCT	58	30	28		L-PRP shows similar results to that of CS in most clinical aspects. Pain and ROM may show more significant improvement with L-PRP	0 (L-PRP)
Shams *et al.* (30)	PRCS	40	20	20		P-PRP shows better clinical outcomes at 3 months FU over CS. No statistically significant better results after 6 months	+ (P-PRP)
von Wehren *et al.* (31)	TS	50	25	25		P-PRP shows better clinical outcomes at 3 months FU over CS. No statistically significant difference after 6 months	+ (P-PRP)
Kesikburun *et al.* (25)	RCT	40	20		20	At 1-year FU, L-PRP was no more effective in improving the quality of life, pain, disability and ROM over placebo	– (L-PRP)
Schwitzguebel *et al.* (26)	RCT	80	41		39	P-PRP did not improve tendon healing or clinical scores compared with saline injections	– (P-PRP)

+, support the use of PRP; –, does not support the use of PRP; 0, neither support nor against PRP use.
FU, follow-up; PRCS, prospective randomized controlled study; TS, therapeutic study.

rates were significantly lower (47). Encouraged by these results, their second study examined patients with large to massive rotator cuff tears. Again, they found that P-PRP augmentation significantly increased the quality of the repaired supraspinatus tendon, decreased retear rate and improved functional scores. Despite these results, and nonintuitively, augmentation did not translate into improved clinical outcomes at 1 year (46).

Another prospective randomized study published by D'Ambrosii *et al.* aimed to compare the efficacy of L-PRP augmentation to surgery alone on clinical outcomes of 40 patients treated for degenerative supraspinatus full-thickness tears. In contrast to the study by Jo *et al.*, they found that the PRP group had a reduction in pain and more rapid mobilization during the short term, but tendon healing and retear rates as assessed by ultrasound were the same between groups (49).

In contrast to both groups above, an Australian group published negative results of P-PRP in two RCTs comparing short-term and mid-term clinical and radiographic outcomes of the patients treated arthroscopically for supraspinatus repair with and without P-PRP. In both studies, they applied two doses of P-PRP at the tendon repair site 7 and 14 days after surgery. In the short term (16 weeks), they found that the addition of P-PRP did not improve early functional recovery, ROM, strength or influence pain scores (50). In the mid-term (range: 36–51 months), they found that P-PRP was beneficial in only one parameter (pain-free abduction strength), while no difference was found in tendon quality or retear rates based on MRI. As tendon quality and retear rates were the primary outcomes, their study did not support the use of P-PRP augmentation for producing a more robust tendon repair (51).

Flury *et al.* investigated intraoperatively applied P-PRP in 120 patients during arthroscopic double-row repair of supraspinatus tendon ruptures on clinical and patient-reported outcomes. Sixty patients were treated with PRP injections applied to the footprint, while the other 60 were treated with a local anesthetic injection to the subacromial space. No significant effect was found for clinical or patient-reported outcomes up to 24 months after arthroscopic rotator cuff repair (52).

In another prospective randomized study with a 5 year follow-up, 54 patients were randomized, and the clinical outcomes of 51 patients (25 control and 26 P-PRP) and the structural outcomes of 44 patients (22 control and 22 PRP) were analyzed during rotator cuff repair of small and medium supraspinatus tears. Liquid P-PRP was prepared by apheresis with autologous thrombin and applied to the tendon-to-bone interface after single-row supraspinatus repair. No significant difference in clinical outcomes or imaging was found at 60 months follow-up (53).

Pandey *et al.* conducted a level 1 study in 102 patients (P-PRP group, 52 patients; control group, 50 patients) with medium- and large-sized degenerative posterosuperior tears with 2 years minimum follow-up. After arthroscopic single-row repair, moderately concentrated P-PRP was delivered over the tendon at the site of the repaired cuff. These authors found that P-PRP accelerated the vascularity of the rotator cuff and surrounding tissues in the early phase of recovery with superior structural healing. Moreover, the retear rate was significantly lower for large tears in the P-PRP group compared to the group with surgery alone (54).

As in the studies of the use of PRP in rotator cuff tears without surgery, the heterogeneity of the outcomes of these studies may be influenced by a wide range of PRP preparations, application methods, tear size and repair techniques. Jo *et al.* used their own technique of PRP gel (46, 47), the Australian group and Flury *et al.* used the Arthrex (Naples, FL, USA) system (50, 51, 52), Malavolta *et al.* used a technique with apheresis set (53) and D'Ambrosi *et al.* used the PlasmaxÒ (Biomet Biologics, Warsaw, IN, USA) (49). Regarding the application methods, in most of the studies, PRP was given at the tendon repair site at the end of the procedure (46, 47, 49, 53, 54), but it was also applied in two doses postoperatively at days 7 and 14 (50, 51), and partially into the repair site combined with subacromial injection (52). Tear size was small to medium

(53), medium to large (47, 49, 54), large to massive (46) and all tear sizes (52). The repair techniques were double row (46, 47, 50, 51, 52), single row (53, 54) or not described (49). The postoperative protocol was generally similar, with 4-6 weeks of immobilization in an abduction pillow allowing passive movements. As can be seen, despite level 1 studies related to the effectiveness of PRP as an adjunct during rotator cuff surgery, there remains a tremendous amount of heterogeneity notwithstanding most of the studies showing favorable results.

The authors conclude that some of the studies currently published, support the use of P-PRP and L-PRP as augmentation after repair of medium-to-large tears. Please see Table 2 for more details.

PRP in adhesive capsulitis

Adhesive capsulitis (AC), also known as 'frozen shoulder', is a frustrating disorder with an incidence in the general population from 2% to 5%, while the prevalence of concomitant diabetes has been reported as high as 72% (55, 56). The main reported complaints of the patients with AC are pain and limited ROM depending on the stage of the disorder, and while all planes of motion are reduced, external rotation in adduction is especially affected (57). While there are many types of treatments, CS administration followed by physical therapy is the most commonly prescribed (58). PRP injections have recently gained popularity because several studies have shown anti-inflammatory qualities by decreasing inflammatory cytokines within the tissue after injection (59, 60).

The first report in the literature for P-RP in AC was a case report by Aslani *et al.* in 2015. A 45-year-old man with two injections of P-RP was treated, at baseline and after 4 weeks. They reported significant improvements in pain, ROM and Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire after treatment (61).

Subsequently, a randomized controlled study conducted by Ünlü *et al.* included 32 patients with AC. The treatment group received three L-PRP injections every 2 weeks, while the other group received saline in the same frequency. These authors found that L-PRP injections were significantly more effective than the saline-injected group, both in pain reduction and in disability, and with concomitant improvements in ROM (62).

Another prospective cohort study by Barman *et al.* with 55 patients compared the effectiveness of P-PRP vs CS in patients with AC. They found that a single dose of P-PRP was more effective than CS at 12 weeks follow-up for pain, disability and shoulder ROM (63).

A controlled laboratory study and cohort study reported by Lee *et al.* clinically evaluated the safety and efficacy of P-PRP injection in patients with AC and assessed the *in vitro* effects of P-PRP on synoviocytes with or without inflammation. Fifteen patients with AC received an ultrasound-guided intra-articular P-PRP injection and were observed for 6 months. In this group, P-PRP decreased pain and improved shoulder ROM and function comparable to CS. Moreover, they found that P-PRP decreased proinflammatory cytokines only during the inflammatory phase of the condition (64).

A randomized comparative study conducted in New Delhi, India, analyzed 180 patients with AC. The authors divided the patients in three groups: (i) patients treated with a single injection of CS (ii) patients with a PRP injection (preparation not defined) and (iii) patients with ultrasound therapy. They found that at 6 weeks, PRP showed statistically significant improvements over ultrasonic therapy for pain and QuickDASH, and at 12 weeks a statistically significant improvement was observed

Table 2 Effectiveness of PRP in augmentation of rotator cuff tear repairs.

Study	Study design	Patients			Tear type	Outcome	Use of PRP
		Total	PRP	Control			
Jo *et al.* (46)	RCT	48	24	24	Large to massive	P-PRP significantly improved structural outcomes. No significant difference in clinical outcomes except the overall shoulder function after 1-year FU	+ (P-PRP)
Jo *et al.* (47)	RCT	74	37	37	Medium to large	P-PRP significantly improved the structural quality but not the speed of healing	+ (P-PRP)
D'Ambrosi *et al.* (49)	RCT	40	20	20	Medium to large	L-PRP leads to a reduction in pain during a short-term follow-up	+ (L-PRP)
Wang *et al.* (50)	RCT	60	30	30	Full thickness	P-PRP treatment does not improve early tendon–bone healing or functional recovery	– (P-PRP)
Ebert *et al.* (51)	RCT	60	30	30	Full thickness	Maximal abduction strength was greater in the midterm after P-PRP. Repeated P-PRP has no additional benefit to tendon integrity	0 (P-PRP)
Flury *et al.* (52)	RCT	120	60	30 RV	All tear size	No significantly improved function at 3, 6 and 24 months after arthroscopic repair compared with control patients	–
Malavolta *et al.* (53)	RCT	54	26	25	Small to medium	P-PRP did not promote better clinical or structural results at 60-month follow-up	– (P-PRP)
Pandey *et al.* (54)	RCT	102	52	50	Medium to large	P-PRP improves clinical and structural outcome in large cuff tears at minimum 2-year FU	+ (P-PRP)

+, support the use of PRP; –, does not support the use of PRP; 0, neither support nor against PRP use.
FU, follow-up; RV, ropivacaine.

Table 3 Effectiveness of PRP in adhesive capsulitis.

Study	Study design	Patients enrolled					Outcome	Use of PRP
		Total	PRP	CS	UT	Control		
Aslani *et al.* (61)	CR	1					60% improvement of diurnal shoulder pain. Two-fold improvement for ROM and more than 70% improvement for function	+
Ünlü *et al.* (62)	RCT	32	17			15	L-PRP was effective in both pain and disability and improved ROM	+ (L-PRP)
Barman *et al.* (63)	PCS	55	28	27			P-PRP was more effective than CS in terms of improving pain, disability, and ROM in 12 weeks FU	+ (P-PRP)
Lee *et al.* (64)	CLSCS	30	15	15			P-PRP decreased pain and improved shoulder ROM and function comparable with that of a corticosteroid	+ (P-PRP)
Kothari *et al.* (65)	RCT	180	62	60	58		Single injection of PRP (preparation not defined) is effective and better than CS or ultrasonic therapy	+
Çaliş *et al.* (66)	ICS	9					Significant improvements in VAS scores, Shoulder Pain and Disability Index scores and ROM in all time points when compared with baseline	+

+, support the use of PRP.
CLSCS, controlled laboratory study and cohort study; CR, case report; FU, follow-up; ICS, interventional case series; PCS, prospective cohort study; UT, ultrasound therapy.

over both ultrasonic and CS therapy in active and passive ROM of the shoulder, pain and QuickDASH (65).

Çalış *et al.* also studied the effect of PRP (product unclear) in nine patients in an interventional case series. PRP was given at baseline and at 2 weeks, and patients were followed for 12 weeks. Patients had significant improvements in the VAS score, Shoulder Pain and Disability Index scores and ROM (66).

Based on the evidence of these studies, the use of the PRP is supported in the diagnosis of AC (61, 62, 63, 64, 65, 66). Nevertheless, there are limitations of these studies. The use of PRP occurred during different stages, with different comparison groups and different extents of efficacy. While three studies did not describe the stage of AC in patients in the study (61, 63, 66), the New Delhi study included patients from all stages (65), Lee *et al.* included patients from inflammation stage only (stage I) (64) and Ünlü *et al.* included patients in the frozen stage (stage II) (62). In three studies, PRP was compared with CS (63, 64, 65), of which two proved PRP to be superior to CS (63, 65) while the other was equivocal (64). Two other studies compared the effectiveness of PRP with no control group (61, 66) and another with saline (62).

Therefore, in line with the encouraging results of P-PRP and L-PRP in AC, the authors believe that PRP sub-groups may be used in patients with AC, although there is a need for more high-quality controlled studies in order to recommend it to be a part of standard protocol or even guidelines. Please see Table 3 for more details.

PRP in subacromial impingement syndrome

Subacromial impingement syndrome (SAIS), while difficult to define, is nevertheless a commonly diagnosed shoulder disorder (67). The first-line treatment is conservative and includes nonsteroidal anti-inflammatory drugs, CS injection and physical therapy, which yields satisfactory results in 60% of cases (68). As with CS in the treatment of SAIS, the use of PRP has gained popularity and has also been investigated.

Nejati *et al.*, in a level 1 study, investigated the role of L-PRP vs exercise therapy in the treatment of SAIS. Sixty-two patients were randomized into two groups receiving either L-PRP or exercise therapy and subsequently followed for 6 months. Both treatments were shown to be effective in pain reduction and increased shoulder ROM, but exercise proved to be more effective than L-RP (68).

PRP (probably L-PRP) effectiveness was compared to the CSs in a study with 60 patients by Say *et al.* (69). Similarly to Nejati *et al.*, patients were followed for 6 months and evaluated with the Constant score, VAS and ROM. CSs

Table 4 Effectiveness of PRP in subacromial impingement syndrome.

Study	Study design	Patients enrolled					Outcome	Use of PRP
		Total	PRP	EG	ST	PT		
Aslani *et al.* (61)	CR	1					60% improvement in diurnal shoulder pain. Two-fold improvement for ROM and more than 70% improvement for function	+
Nejati *et al.* (68)	RCT	62	31	31			L-PRP and exercise therapy were effective in reducing pain and disability, with exercise therapy proving more effective	– (L-PRP)
Say *et al.* (69)	RCT	60	30		30		Steroid was more effective than PRP (probably L-PRP) in terms of the Constant score and VAS at 6 weeks and 6 months	– (L-PRP)
Pasin *et al.* (70)	RCT	90	30		30	30	All three treatment modalities were similarly effective methods of physical therapy	0

Note. +, support the use of PRP; –, does not support the use of PRP; 0, neither support nor against PRP use.s
CR, case report; EG, exercise group; FU, follow-up; PT, physical therapy; ST, steroid.

were more effective than PRP in both the Constant score and VAS at 6 weeks and 6 months follow-up.

Pasin *et al.* compared the effectiveness of three groups of the treatment in the SAIS. Ninety patients with SAIS were randomized into three groups consisting of L-PRP injection, CS injection and physical therapy. Patients were followed for 8 weeks, and VAS score, Shoulder Disability Questionnaire, QuickDASH questionnaire and the University of California, the Los Angeles Shoulder Rating Scale and the Short Form 36 (SF-36) were measured. They found that all three treatments showed efficacy but recommended the use of physical therapy as it is noninvasive and cost-effective (70).

Therefore, based on the current literature, the effectiveness of PRP was similar or inferior to other modalities, and thus its use in the treatment of the SAIS is not recommended. Please see Table 4 for more details.

Omarthrosis PRP

To date, there is no single study studying the effect of PRP in omarthrosis. Therefore, PRP cannot be recommended in these patients until sufficient data have been published.

Safety of PRP application in the shoulder

There are few studies examining the safety independent of the efficacy of PRP treatment to the shoulder. A prospective study by Dyson-Hudson *et al.* tested the safety and potential treatment of L-PRP for the pain in the shoulder in wheelchair patients with spinal cord injury. Six wheelchair patients (three paraplegia and three tetraplegia) who had chronic shoulder pain due to rotator cuff disease and failed conservative treatment for at least 6 months were treated with ultrasound-guided L-PRP and a stretching and strengthening exercise program was prescribed. They found that L-PRP was safe and provided improvements in shoulder pain outcomes at 24 weeks (71).

Another meta-analysis by Wang *et al.* assessed the safety of PRP in arthroscopic full-thickness rotator cuff repair. They found that PRP was safe and effectively improved the short-term outcomes following arthroscopic repair of full-thickness rotator cuff tears (72). Another study by Prodromos *et al.* looking at the efficacy and safety of L-PRP in rotator cuff tears found that dual injections of L-PRP into the shoulder was safe and effective in patients that failed conservative treatment (73). However, Schwitzguebel *et al.*, in their RCT, found that P-PRP was associated with higher incidence of adverse events such as pain, frozen shoulder and extension of the lesion compared to saline at more than 1 year of follow-up (26).

Based on the current literature, we can conclude that there are no data that indicate a major clinical risk after application of PRP into the shoulder and its use is considered relatively safe.

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