

REVIEW

PLATELET-RICH PLASMA INJECTION IN NON-OPERATIVE TREATMENT OF PARTIAL-THICKNESS ROTATOR CUFF TEARS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: Partial-thickness rotator cuff tears have a high prevalence in older people. Treatment for such tears remains controversial. Platelet-rich plasma has recently attracted attention for treating partial-thickness rotator cuff tears, due to its regenerative characteristics. However, the results of application of platelet-rich plasma in non-operative treatments are unclear. The aim of this review is to evaluate the effects on shoulder function improvement and pain relief of platelet-rich plasma injection in partial-thickness rotator cuff tears, at different follow-up times (3–6 weeks, 8–12 weeks, and more than 24 weeks after treatment) compared with placebo or corticosteroids.

Design: A systematic review and meta-analysis.

Methods: Several databases, including PubMed, EMBASE, and Cochrane, were searched. Eleven studies met the inclusion criteria for the meta-analysis. The quality of research was evaluated using the Cochrane risk-of-bias tool. The effectiveness of platelet-rich plasma was calculated as the difference between baseline measurements and post-injection outcomes. The standardized mean difference was used to compare different outcome scales or questionnaire measurements. Statistical analysis was performed using Stata 15.0.

Results: The analysis included 11 studies, with a total of 641 patients (318 treated with platelet-rich plasma and 323 controls). Compared with placebo, platelet-rich plasma exhibited significantly better effects on shoulder function improvement and pain relief at all 3 follow-up times. Compared with other conservative treatments, platelet-rich plasma exhibited significantly better effects on shoulder function and pain relief at 8–12 weeks and at more than 24 weeks after treatment.

Conclusion: This review showed positive effects on shoulder function improvement and pain relief of the use of platelet-rich plasma in treating partial-thickness rotator cuff tears, especially in relatively late stages of follow-up (more than 8 weeks) after treatment.

LAY ABSTRACT

Partial-thickness rotator cuff tears are common, especially in older people, and can cause shoulder pain and movement limitation. Platelet-rich plasma is a platelet concentrate made from autologous blood, which may have anti-inflammatory and healing effects. This systematic review and meta-analysis collected data from existing studies to determine the specific effects of platelet-rich plasma injection on partial-thickness rotator cuff tears. The results showed that, compared with both no treatment and other conservative treatments, platelet-rich plasma reduced pain and improved shoulder function when used to treat partial-thickness rotator cuff tears. Meanwhile, the effects were most significant at 8–12 weeks and at more than 24 weeks after treatment.

Key words: partial-thickness rotator cuff tear; platelet-rich plasma; shoulder function; shoulder pain.

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A partial-thickness rotator cuff tear (PTRCT) is defined as the disruption of tendon fibres and is characterized by pain and activity limitation, occurring due to degenerative factors and overhead movements. A study by Milgrom et al. reported that the prevalence of PTRCTs in patients over the age of 60 years was 26%, compared with 4% under the age of 40 years (1). Another study showed that the prevalence of PTRCT in overhead athletes (such as baseball athletes, volleyball athletes, etc.) was 40% in the dominant shoulder (2). There are various classification systems for PTRCTs, but there is, as yet, no consensus on the optimal system according to clinical studies (3–6). Studies using various different classification systems have shown that there is no simple treatment strategy for PTRCTs, and the treatment options

are controversial. Histological studies have shown that PTRCTs cannot heal themselves over time (7, 8), and open or arthroscopic surgical treatments to repair the damage are effective for many patients. Non-operative management is usually the first option for treating PTRCTs, and these methods mainly include rest, activity modification, pain medication, anti-inflammatory drugs, corticosteroid injections, and physical therapy. However, such treatments are limited, since they do not impact the progression of PTRCTs. Recent reports have also questioned their efficacy and suggested that they merely relieve clinical symptoms, but do not enhance tendon healing in the injured rotator cuff (9, 10). Therefore, further studies are needed to search for an effective treatment for tendon healing in PTRCTs.

Platelet-rich plasma (PRP) is a platelet concentrate derived from autologous whole blood with a high concentration of platelets; PRP contains 3- to 6-fold more platelets than whole blood (11–13). The granules in platelets can release high levels of growth factors, including vascular endothelial growth factor (VEGF), transforming growth factor β (TGF- β), and platelet-derived growth factor (PDGF) (14); as such, PRP has the potential to enhance the healing of injured or degenerated tendons and is currently being tested widely in different fields of medicine (15). In the last few years, an increasing number of studies has focused on the use of PRP injection in treatment aiming to repair PTRCTs. Clinical studies on the use of PRP in conventional non-operative treatments are controversial, and most studies have focused on full-thickness rotator cuff tears. While the use of PRP in the repair of PTRCTs is still in the exploratory stage, it has already shown positive results in improvement of shoulder function and pain relief, with a potential effect of tendon healing (16–18).

The aim of this review is to evaluate data from randomized controlled studies of the effects on shoulder function improvement and pain relief of PRP injection for treatment of PTRCT, measured at different follow-up times (3–6, 12, and 24 weeks after treatment), compared with placebo or corticosteroids.

METHODS

Inclusion and exclusion criteria

Inclusion criteria were: (i) PTRCT; (ii) diagnosis based on magnetic resonance imaging (MRI) or sonography; (iii) application of PRP; (iv) reported outcomes, including function improvement and pain relief; (v) randomized controlled design.

Exclusion criteria were: (i) the use of surgery or other treatment combined with PRP; (ii) diagnosis not based on MRI or sonography findings; (iii) full-thickness tear

of the rotator cuff; (iv) unavailable mean and standard deviation (SD) of outcomes.

Search strategy

The authors independently screened the literature, extracted data, and performed crosschecks following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic databases, including PubMed, EMBASE, and Cochrane, were searched using the following medical subject heading (MeSH) terms: “Platelet-Rich Plasma” (MeSH) AND “Rotator Cuff” (MeSH) as keywords. Articles were identified through a manual search of the reference lists of the relevant articles. The literature search spanned the date of database inception to 31 December 2021. Two reviewers independently reviewed the full texts of all potentially relevant articles to identify articles meeting the eligibility criteria. The individually recorded decisions of the 2 reviewers were then compared, and a third reviewer resolved dissimilarities in the decisions.

Data items

The following information was obtained from each article identified: characteristics of rotator cuff tears, follow-up duration, outcome measurements, and PRP preparation and application schemes.

Risk-of-bias assessment

The quality of RCTs was evaluated using the Cochrane risk-of-bias tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions (19). Possible biases are divided into 5 domains (selection bias, performance bias, detection bias, attrition bias, and reporting bias) and a generalized category of other biases. All items were independently assessed by 2 authors. Each outcome within a study across domains and each outcome across the studies was rated as having “Low risk”, “Unclear risk”, or “High risk” of bias. The kappa statistic determined inter-rater reliability to evaluate the strength for the risk-of-bias assessments. Discussions with the corresponding author were made to solve the disputes.

Statistical analysis

The effectiveness of PRP was calculated as the difference between baseline measurement and post-injection outcome. The standardized mean difference (SMD) was adopted to properly compare different outcome scales or questionnaire measurements. A random-effects model was used to calculate the pooled SMD with a 95% confidence interval (95% CI). Heterogeneity was assessed by I-square. An I-square > 50% was recognized as significant heterogeneity. The

analysis was performed using Stata 15.0 (StataCorp LP, College Station, TX, USA). All *p*-values were 2-sided, and the significance level was set at 5% except for the test of between-study heterogeneity. Sensitivity analysis was performed by removing the relative low-quality studies and re-performing the meta-analysis. Publication bias was not analysed because of the limited number (< 10) of studies included in each analysis.

RESULTS

Search results

With the search terms listed above, 26 articles were initially retrieved. Five duplicates were excluded using EndNote X9. 3 Thomson ResearchSoft. Citations that were non-compliant with the inclusion criteria were excluded after screening their title and abstract. The full text of the remaining 16 citations was screened, revealing 3 citations did not have a control group, 1 citation did not apply singly, and 1 citation did not express the outcome with mean and SD. A final total of 11 articles were selected for this systematic review and meta-analysis (Fig. 1).

Study characteristics

All 11 included studies were published between 2013 and 2021. A total of 641 patients were included (318 patients in the PRP group and 323 in the control group). The control groups in the included studies were as

follows: 3 studies used placebo (saline or dry needle) (20–22); and 8 used conservative treatments (corticosteroids injection or physical therapy) (23–30). Ten studies prepared PRP via centrifugation. Three studies applied multiple injections at different intervals, while another 8 studies applied injections only once. The main characteristics of the 11 included studies are summarized in Tables I and II.

Risk-of-bias assessment

The graph and summary of the risk-of-bias are shown in Fig. 2. Most of the higher or unclear risks of bias were generated in the allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. A possible reason is that it is difficult to blind patients and operators to drawing blood for PRP preparation.

Shoulder function

Shoulder function was reported in all 11 studies. The shoulder function was significantly improved in the PRP group compared with in the control group in all 3 stages (Fig. 3A). Subgroup analysis revealed that PRP was more effective in shoulder function improvement than placebo in all 3 stages (Fig. 3A). However, the PRP group exhibited significant improvements in shoulder function compared with other conservative treatments in 8–12 weeks (SMD=0.40, 95% CI (0.17, 0.62)) and more than 24 weeks (SMD=0.31, 95% CI (0.05, 0.56)) (Fig. 3A).

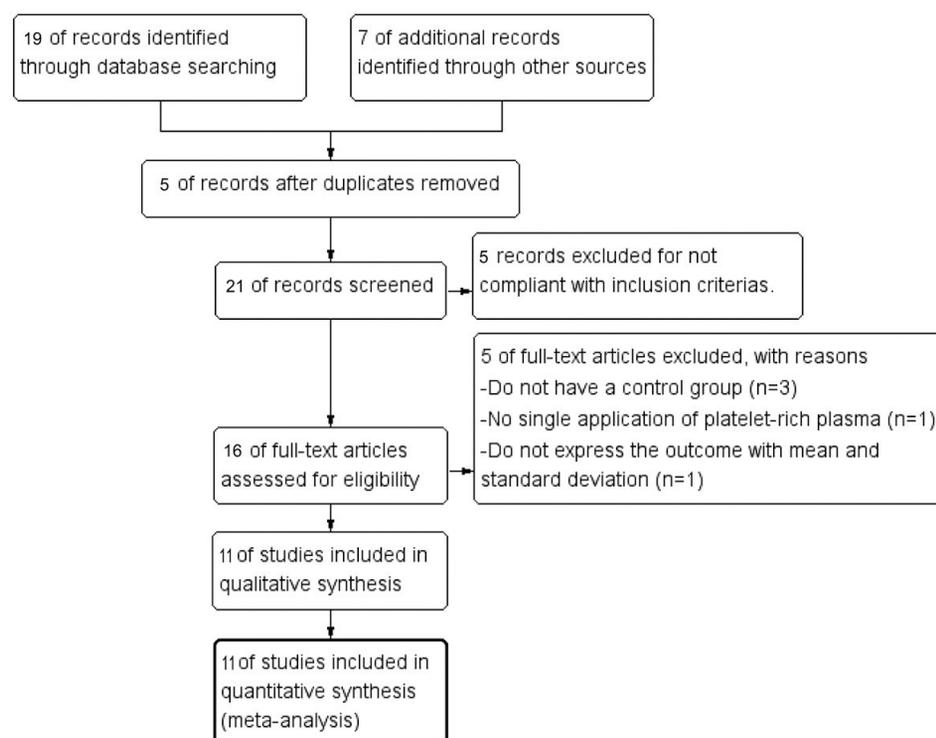


Fig. 1. Flow diagram of study inclusion.

Table I. Research on the non-operative treatment of partial-thickness rotator cuff tears (PTRCTs) with platelet-rich plasma (PRP)

Study	Patients (PRP/control)	Control	Inclusion criteria			Outcome measurement	
			Tear time, months	Size	Follow-up duration	Shoulder function	Pain
Rha et al. 2013 (17)	16/14	Placebo (dry needles)	> 6	< 1.0 cm	6 months	SPADI	Pain in SPADI
Ilhanli et al. 2015 (26)	30/32	Physical therapy	Not mentioned	Not mentioned	12 months	DASH score	VAS score
von Wehren et al. 2016 (22)	25/25	Corticosteroids	> 2	Not mentioned	6 months	SST score, CS, ASES score	VAS score (specific data were not given)
Shams et al. 2016 (21)	20/20	Corticosteroids	> 3	Not mentioned	6 months	SST score, CS, ASES score	VAS score (specific data were not given)
Cai et al. 2019 (16)	45/47	Placebo (saline)	< 6	< 1.0 cm	1 year	CS, ASES score	VAS score
Schwitzguebel et al. 2019 (18)	41/39	Placebo (saline)	> 6	Not mentioned	> 12 months	ASES score	VAS score
Ibrahim et al. 2019 (25)	15/15	Corticosteroids	Not mentioned	Not mentioned	7 months	SDQ score	VAS score
Cory et al. 2020 (19)	52/47	Corticosteroids	> 3	Not mentioned	1 year	ASES score, WORC score	VAS score
Sari et al. 2020 (20)	30/30	Corticosteroids	> 3	Grade 1	24 weeks	ASES score, WORC score	VAS score
Dadgostar et al. 2021 (23)	30/28	Corticosteroids	> 3	Not mentioned	3 months	WORC score, DASH score	VAS score
Thepsoparn et al. 2021 (24)	15/16	Corticosteroids	> 3	Not mentioned	6 months	OSS	VAS score

SPADI: Shoulder Pain and Disability Index; SST: simple shoulder test; CS: Constant (Murley) score; ASES: American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; WORC: Western Ontario Rotator Cuff; SDQ: Strength and Difficulties Questionnaire; DASH: Disabilities of the Arm, Shoulder and Hand; OSS: Oxford Shoulder Score; VAS: visual analogue scale.

Pain relief

Pain relief was reported in all 11 studies, while only 9 showed a specific mean and SD. One of them reported in Pain score of Shoulder Pain and Disability Index (SPADI) (21), and another 8 reported in visual analogue scale (VAS) score. The pain was significantly released in the PRP group than in the control group in 8–12 weeks and more than 24 weeks (Fig. 3B). Subgroup analysis revealed that PRP was more effective in pain relief than placebo in all 3 stages (Fig. 3B). Meanwhile, compared with other conservative treatment, PRP exhibited better effects in pain relief in 8–12 weeks (SMD=−0.36, 95% CI (−0.62, −0.11)) and more than 24 weeks (SMD=−0.62, 95% CI (−0.95, −0.30)) after treatment (Fig. 3B).

the relatively low-quality studies and re-performing the meta-analysis. As shown in Fig. 2, the risk-of-bias in the included studies exists mainly in allocation concealment, blinding of participants and personnel, and blinding of outcome assessment, which is because PRP injection is an invasive treatment and PRP needs to be prepared with autologous blood. Thus, we selected the relatively low-quality studies ignoring the 3 items, and 2 studies (von Wehren et al. 2016 and Ibrahim et al. 2019 et al.) (22, 25) were selected. Meanwhile, the 2 studies contribute little to the analysis of pain relief, sensitivity analysis was performed only on shoulder function improvements analysis in all 3 stages. As shown in Fig. 4, all results are consistent with Fig. 3, indicating that the analysis results are stable.

Sensitivity analysis

Because of the large heterogeneity between studies, the sensitivity analysis was performed by removing

This systematic review and meta-analysis focused on the effect of PRP on the non-operative treatment of

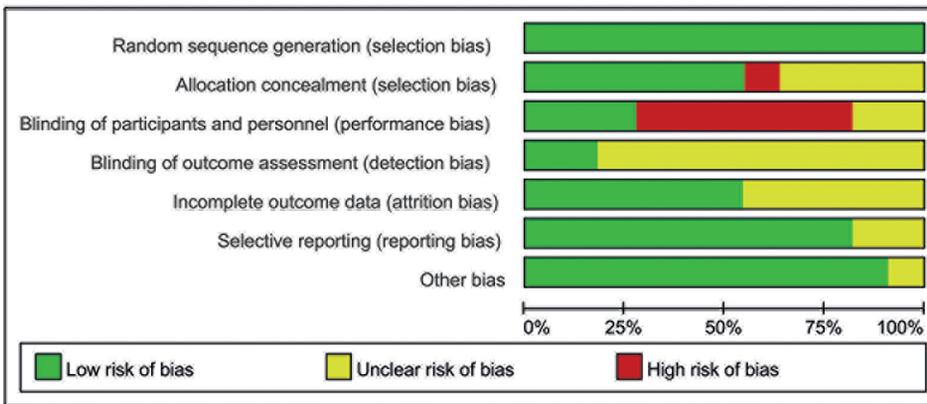
DISCUSSION

Table II. Platelet-rich plasma (PRP) preparation and application schemes in studies included in the review

Study	PRP volume, ml	PRP preparation method	Preparation kit	Application scheme	Injection method
Rha et al. 2013 (17)	3	Centrifugation	Prosys PRP Platelet Concentration System (Tozaiholdings)	2 injections, 4-week interval	Ultrasound-guided injection
Ilhanli et al. 2015 (26)	6	Centrifugation	Not mentioned	1 injection	Not mentioned
von Wehren et al. 2016 (22)	5	Centrifugation	Arthrex Centrifuge (Rotofix)	3 injections, 7-day interval	Subacromial injection
Shams et al. 2016 (21)	2–2.5	Centrifugation	MyCells Autologous Platelet Preparation System (ProTech)	1 injection	Subacromial injection
Cai et al. 2019 (16)	5–6	Centrifugation	Labofuge 400R (Heraeus)	4 injections, 7-day interval	Ultrasound-guided subacromial injection
Schwitzguebel et al. 2019 (18)	2	Centrifugation	RegenKit BCT (Regen Lab)	1 injection	Ultrasound-guided subacromial injection
Ibrahim et al. 2019 (25)	2	Centrifugation	Not mentioned	1 injection	Not mentioned
Cory et al. 2020 (19)	3–5	Centrifugation	RegenLab (Lausanne)	1 injection	Ultrasound-guided subacromial injection
Sari et al. 2020 (20)	5	Centrifugation	Not mentioned	1 injection	Ultrasound-guided subacromial injection
Dadgostar et al. 2021 (23)	3	Not mentioned	ROOYA GEN (Arya Mabna Tashkhis Co.)	1 injection	Ultrasound-guided subacromial injection
Thepsoparn et al. 2021 (24)	5	Centrifugation	ACP Double Syringe System (Arthrex)	1 injection	Ultrasound-guided subacromial injection

Author	von Wehren et al. 2016	Thepsoparn et al.	Shams et al. 2016	Schwitzgebel et al. 2019	Sari et al. 2020	Rha et al. 2013	Ihranti et al. 2015	Ibrahim et al. 2019	Daogostar et al. 2021	Cory et al. 2020	Cal et al. 2019
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment (selection bias)	-	+	?	+	+	+	?	?	+	+	?
Blinding of participants and personnel (performance bias)	-	?	-	+	+	-	-	-	?	+	?
Blinding of outcome assessment (detection bias)	?	?	?	+	?	+	?	?	?	?	?
Incomplete outcome data (attrition bias)	?	?	?	+	+	+	+	?	+	+	?
Selective reporting (reporting bias)	?	+	+	+	+	+	+	?	+	+	+
Other bias	+	+	+	+	+	+	+	?	+	+	+

A. Risk of bias summary.



B. Risk of bias graph.

Fig. 2. Risk-of-bias (A) summary and (B) graph. Green: low risk-of-bias; red: high risk-of-bias; yellow: unclear risk-of-bias.

PTRCT. The results of the analysis revealed statistically significant differences in the following aspects:

- PRP exhibited significantly better improvement in shoulder function and pain relief despite the subgroup analysis.
- Compared with placebo, PRP exhibited significantly better effects on shoulder function improvement and pain relief in all 3 stages.
- Compared with other conservative treatment, PRP exhibited significantly better effects on shoulder function and pain relief at follow-up at 8–12 weeks and more than 24 weeks after treatment.

The application of PRP for tendon-to-bone healing has already been widely adopted, due to acquisition of PRP being convenient and its ability to promote regenerative bioactivity (16). Given these regenerative properties, the application of PRP has attracted the interest of clinicians, especially specialists in osteo-

arthropathy. In the treatment of tendinous injuries, both fundamental experiments and clinical studies have exhibited the great value of PRP (16–18).

PRP can be classified into leukocyte-rich PRP (Lr-PRP) and leukocyte-poor PRP (Lp-PRP) based on the platelet concentration. Animal experiments have shown that high leukocyte levels in PRP could increase the levels of proinflammatory cytokines and weaken the beneficial healing effects of PRP on chronic tendinopathy (31). In addition, Lp-PRP exhibited more significant effects on promoting normal collagen matrix synthesis and decreasing the levels of cytokines associated with matrix degradation than Lr-PRP in degenerative tendons (32–34). Two main methods are generally applied to obtain PRP: 1 is apheresis, which produces purer PRP with higher platelet and lower leukocyte levels (35, 36); the other is centrifugation, which is more widely used, as in all of the studies reviewed in this article, and has the advantages of a lower cost and requiring simpler materials (37). Regarding the reparative effects,

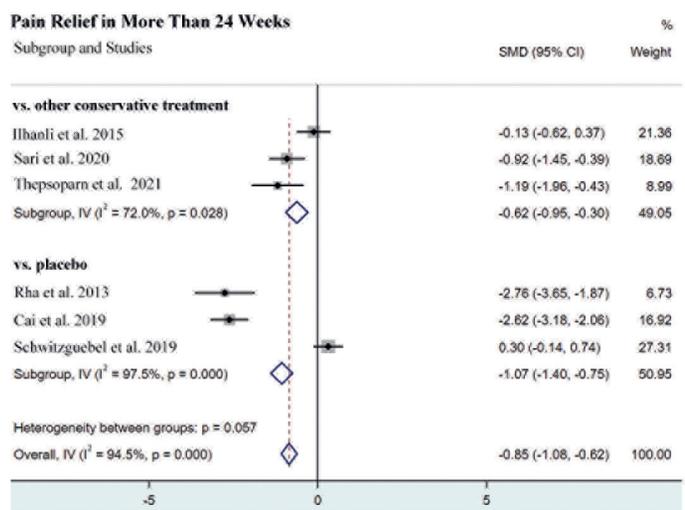
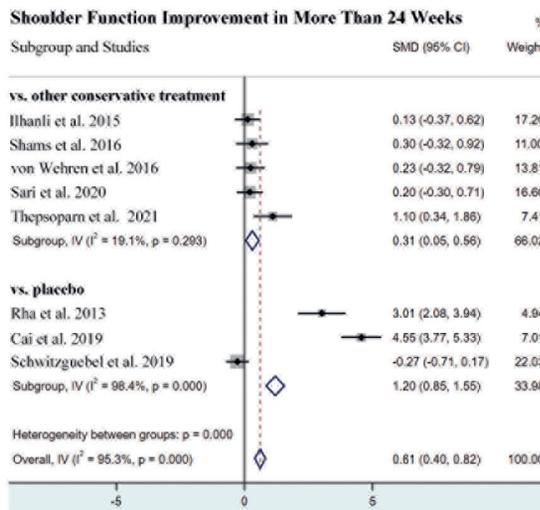
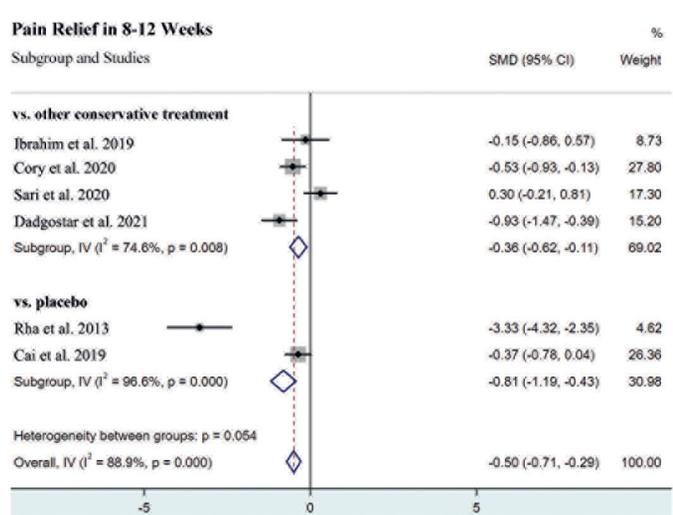
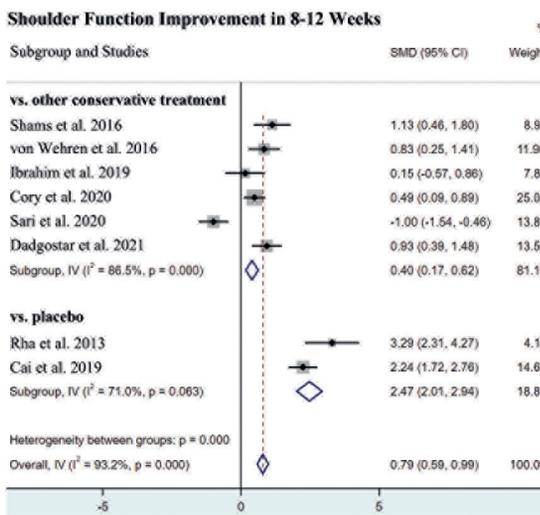
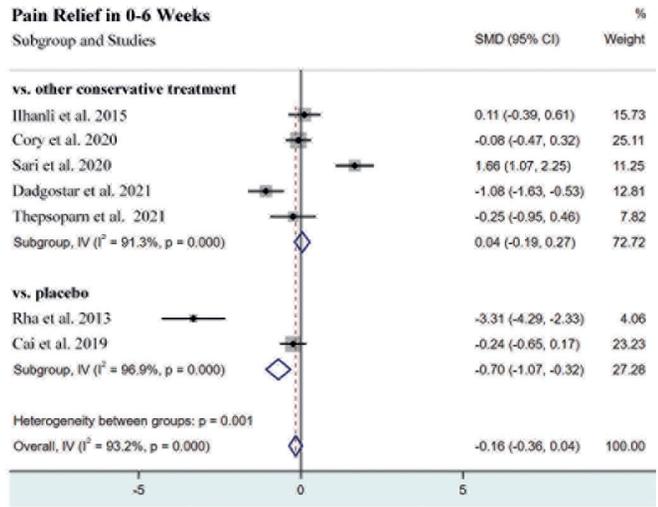
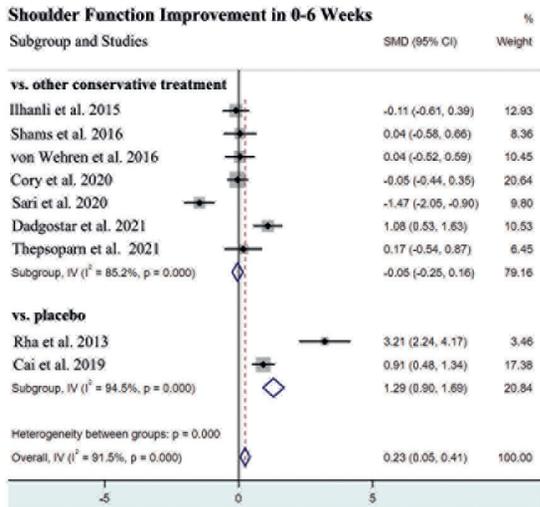


Fig. 3. Forest plot of meta-analysis. (A) Shoulder function improvements. (B) Pain relief.

apheresis is better, due to the lower leukocyte levels. However, when including consideration of cost, the method of choice should be further assessed.

Regardless of the type of method, PRP is prepared from autologous blood; thus it has lower immunogenicity and is safer than traditional drug injections

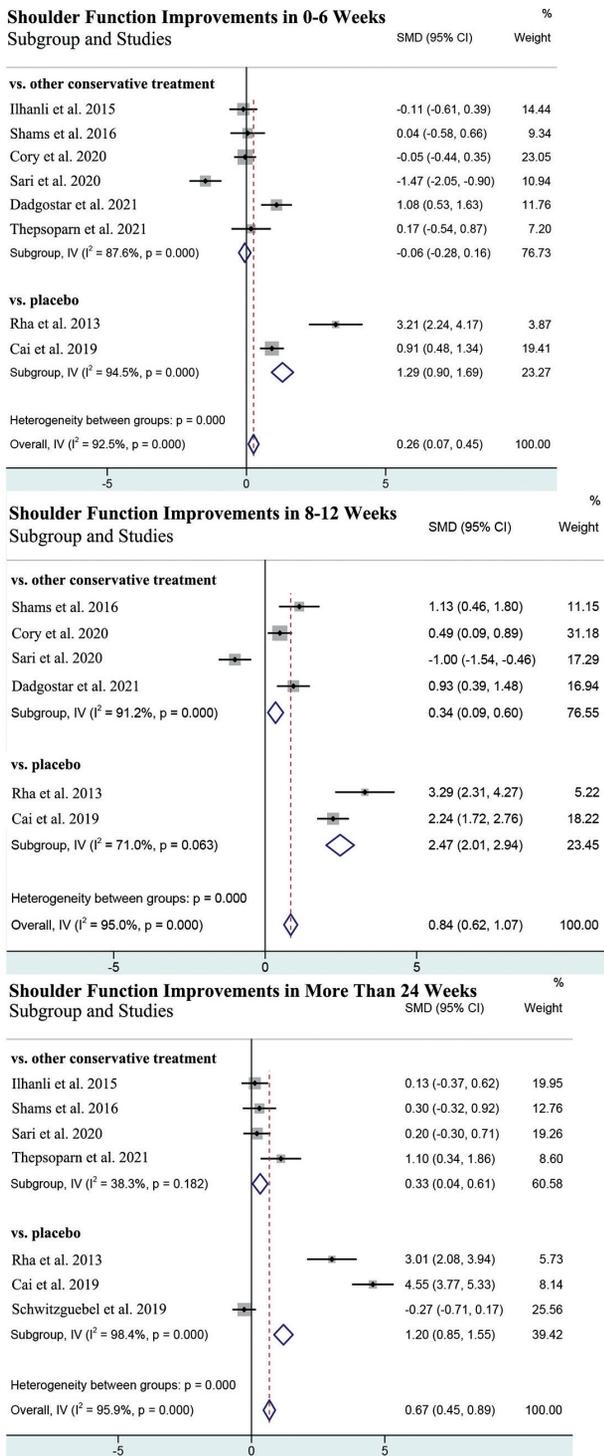


Fig. 4. The sensitivity analysis by removing relatively low-quality studies and re-performing meta-analysis on shoulder function improvements.

(e.g. corticosteroids) without specific adverse effects (15–18). Most studies have shown no adverse events during treatment with PRP (15–18). Regarding the injection method, although injection under ultrasound guidance is highly recommended and exhibits good

efficacy and safety (38), subacromial injection without guidance also shows significant improvements in shoulder function and pain relief (25, 26, 39). However, ultrasound-guided injections might be more precise, safer and more accessible for young physicians to less-experienced practitioners. Both ultrasound-guided and freehand injections are safe and effective, with no evidence that one is better than the other (15–18); hence personal preference and experience should guide the choice of delivery method.

PTRCTs can be classified as articular-side, bursal-side, and intra-tendinous tears, based on the anatomical location of the tear. In general, it is believed that treatments for tears at different locations exhibit different effects and prognoses. More positive results are found for tears on the bursal side, because they can easily be reached by subacromial injection. Kim et al. also found that the treatment of bursal-side tears results in comparable or superior postoperative functional outcomes compared with the treatment of articular-side tears after arthroscopic surgery (40). However, none of the studies in this field have analysed the results of different tear types or included only bursal-side tears. As a result, whether PRP exhibits considerable clinical efficacy at all 3 locations is unclear, and more studies with further analysis based on the tear type are required.

PTRCTs are complex injuries influenced by multiple factors, and the natural history of PTRCTs remains unclear. As a result, studies on the single use of PRP cannot draw reliable conclusions, and the potential of combined uses of PRP might be ignored. In the treatment of PTRCTs, PRP combined with marrow aspirate concentrate (BMAC) and (or) sodium hyaluronate (SH) has been proven effective (20, 41). A recent *in vitro* study found that PRP combined with insulin could promote human adipose-derived stem cells' chondrogenic and osteogenic differentiation (42). Intra-articular injection of PRP combined with mesenchymal stem cells for treating patellofemoral osteoarthritis also resulted in improved joint function (43). Although the feasibility and usage of combined applications should be evaluated in detail, and there are still possibilities for the combined use of PRP, not only in the treatment of rotator cuff tears, but also in other fields of sports medicine.

PRP is prepared from autologous blood, which means it has relatively low immunogenicity. However, there are situations in which it is not suitable to draw autologous blood, such as in patients with anaemia or platelet dysfunction. Jo et al. compared the application of allogeneic and autologous PRP obtained from patients undergoing arthroscopic rotator cuff repair and prepared using a plateletpheresis system with leukocyte removal (44). They showed that allogeneic and autologous PRP had comparable effects

with no adverse events (44), which further broadens the use of PRP and makes it possible for PRP to be commercialized.

Due to individual differences, the space around the injured tendons is different. And in some cases, this space could contain exudates that could affect the PRP concentration. However, studies have found that the proper platelet concentration is 3–6 times above the baseline, and higher levels could exhibit inhibitory effects (11, 12, 36). As a result, increasing the PRP concentration or the number of platelets might not be feasible. Most studies included in this review applied PRP only once. Further research is needed to determine whether repeated application of PRP at suitable intervals could lead to improved effects.

Study limitations and strengths

This review is limited by the relatively few studies comparing PRP with traditional or placebo treatments. Thus it is not possible to draw a robust conclusion regarding the superiority of PRP. Meanwhile, few clinical studies focus on the effects of PRP on rotator cuff healing. Further research into the possible effects is needed.

Previous reviews or meta-analyses of PRP for treatment of rotator cuff tears have not focused solely on PTRCTs; hence the value of PRP in treating PTRCTs has not been analysed in detail. Although some studies have posited that PTRCTs cannot heal themselves over time (7, 8), it is thought that they could heal with proper conservative treatment (38). A meta-analysis published in December 2021 also focused on the application of PRP for PTRCT. It did subgroup analysis of PRP preparation by centrifugation times. However, PRP in their included studies was prepared using kits from different manufacturers (45). Bias due to different centrifugation times appears to be less important than bias due to different manufacturers. Meanwhile, the main objective of analysing the application of PRP is to find a better treatment to replace traditional conservative treatments. This is the first review to focus mainly on the clinical effects of PRP on the non-operative treatment of PTRCTs in the near, medium, and long term after treatment compared with other conservative treatments.

CONCLUSION

This review of studies into the use of PRP injections in non-operative treatments for treatment of PTRCTs, showed improvements in both shoulder function and pain relief, especially at a relatively late stage (12 weeks or more) after treatment. However, due to

the limitations mentioned above, this conclusion is not sufficiently robust and further research is needed.

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Ethical approval

All applicable international, national, and/or institutional guidelines were followed.

The authors have no conflicts of interest to declare.

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