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Original Article

Efficacy and clinical outcomes of platelet-rich plasma for arthroscopic repair rotator cuff tears: a meta-analysis

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Abstract: Background: Platelet-rich plasma (PRP) is used as an innovative clinical therapy, especially for arthroscopic rotator cuff repair. The current literature about PRP for arthroscopic repair rotator cuff tears provides ample but inconsistent data. The purpose of our meta-analysis was to appraise the efficacy and clinical outcomes of PRP use in patients which undergoing arthroscopic rotator cuff repair. Material and method: We carefully searched the Cochrane Library, PubMed, Web of Science, Google Scholar and EMBASE major medical databases for all possible randomized controlled trials which comparing clinical outcomes of arthroscopic rotator cuff repair with or without PRP. Two reviewers selected all studies for inclusion, then assessed methodologic quality of all articles, finally extracted data. Data included outcome scores and re-tears diagnosed with imaging studies. Dichotomous variables were all presented as risk ratios (RRs) with their 95% confidence intervals (CIs), also continuous data were all measured as mean differences with their 95% CIs too. Results: Fifteen randomized controlled trials about PRR use in arthroscopic rotator cuff repair were included in our study, with the patient number ranging from 28 to 88. For all included studies overall methodological quality was high enough. Random-effects analysis showed that the differences were not significant between the PRP and Placebogroups in final re-tear rate (RR, 0.65; 95% CI, 0.40 to 1.06; P=0.08), Constant Scale (WMD, 2.49, 95% CI, -1.58 to 6.57; P=0.23), and University of California at Los Angeles (UCLA) score (WMD, 0.92; 95% CI, -1.29 to 3.13; P=0.41). Conclusions: Our study does not support the use of PRP in arthroscopic repair of full thickness rotator cuff tear, because the re-tear rates and clinical efficacy weresimilar when compared with that of no use PRP. Level of Evidence: Level II, meta-analysis of Level I and Level II studies.

Keywords: Rotator cuff, PRP, platelet-rich plasma, meta-analysis, systematic review

Introduction

It is currently estimated that roughly 250,000 rotator cuff repairs are performed every year in the United States alone [1]. Rotator cuff tears have an adverse effect on daily activities in personal disability and functional restriction. Arthroscopic rotator cuff tear repair surgery are increasing in frequency with improvements in instrumentation and surgeon preference [2]. Although arthroscopic repair for the rotator cuff typically provides satisfactory results [3-5], after large or massive rotator cuff tears repaired arthroscopically, there is still a significant failure-to-heal rate [6]. In spite of the technological changes, the focus of this period has been the biomechanical principles and the optimization of the maintenance strength. Although improving biomechanics may modestly improve healing progress, it seems that biological augmentation of the rotator cuff healing process needs to be investigated to further reduce the failure rates by improving the tendon-to-bone integration [7].

In the last few years, platelet rich plasma (PRP) has been widely used as a biological solution to improve the healing of the rotator cuff tendon. PRP, the most simple autologous blood platelet concentrate, can be obtained by applying direct injection or physical application of PRP matrix scaffold for tissue repair [8-10]. Although different commercially available products have differences, the main growth factor in PRP includ-

ing transforming growth factor beta 1, platelet derived growth factor and vascular endothelial growth factor, hepatocyte growth factor and insulin-like growth factor 1. These autologous growth factors may play an important role in tendon tissue regeneration by increasing the proliferation, collagen synthesis and angiogenesis of tendon cells [1, 10]. At present, there are a lot of basic science and animal data show that PRP has a positive effect on tendon collagen deposition and angiogenesis [11-13].

Although the use of PRP to improve the healing of rotator cuff potential has a strong theoretical basis and interest, but the effectiveness of PRP on clinical is still continuing debate. Clinical trials regarding the use of PRP in arthroscopic rotator cuff repair have shown mixed outcomes [14-25]. Randomized controlled trials are common considered to be the most reliable form of all scientific evidence in the hierarchy of evidence because randomized controlled trials reduce the spurious inferences of causality and bias. Our objective of this meta-analysis was to identify and finally summarize all available evidence to determine the clinical efficacy of arthroscopic rotator cuff repair surgery in patients with confirmed rotator cuff tears that were concomitantly treated along with PRP products.

Materials and methods

Search strategy and criteria

Two investigators (J.S. and X.B.C.) independently and separately searched the Cochrane Library, NCBI PubMed, Web of Science, Google Scholar and EMBASE major medical databases to retrieve all relevant studies published before February 1, 2016. Our search strategy was common based on combinations of medical subject headings (MeSH) and the keywords “rotator cuff tear”, “rotator cuff”, “PRP”, “PRFM”, “platelet rich fibril matrix”, “platelet-rich fibrin”, and “platelet-rich plasma”. No restrictions to specific languages or years of publication were imposed. The “related articles” function for all included studies was also used to broaden our search. Two investigators (P.C.L and Z.Y.) manually examined the entire reference lists of these selected studies to identify all possible relevant studies that were not discovered during our previous overall database searches. The corresponding authors may be contacted only when any necessary additional information of the studies was needed.

Inclusion criteria

1. Prospective studies of Level evidence for I or II; 2. Arthroscopic rotator cuff repair; 3. Studies comparing clinical outcomes with and without PRP application; 4. Longer than 1-month minimum follow-up time; 5. Follow-up examination outcomes presenting at least one of the following measurements: Operative time, Constant score, UCLA scale, SER (Kg), ASES score, DASH score, SST scale, VAS scale, CSA (cross-sectional area), SPADI scale, L’Insalata score, MRI rating, Vascularity score, OSS score, Manual muscle testing ratio, EQ-5D score, WORC score, SF-12 Short Form scale (MCS and PCS), Rotator cuff re-tear rate, complications rate, satisfaction rate, complete healing rate, tendon integrity, intact repair rate and radiographic (MRI, MRA and/or US) follow-up of repaired rotator cuff.

Exclusion criteria

1. Retrospective study; 2. Level III or IV evidence studies; 3. Less than 1-month minimum follow-up time; 4. Studies only reporting clinical outcomes with PRP application; 5. Studies included patients with open or mini-open procedures; 6. Studies involving patients with partial thickness rotator cuff tears

Data extraction

Two readers (J.S. and X.B.C.) reviewed titles and abstracts using the above mentioned selection criteria. Two readers also independently performed the data extraction of all possible variables and outcomes for our interest measurements and the assessment of methodological quality. Any disagreement was resolved by discussion and consensus in two readers. The methodological quality scores of all trials were also assessed by using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.

Outcomes

All eligible studies were carefully reviewed for baseline data, intervention methods and outcome measures. Both subjective and objective clinical functional outcome measurements were fully used to evaluate our final data. The following measures were carefully reviewed in

Table 1. Included studies on platelet-rich plasma clinical applications and their outcomes

First author	Year	Level of Evidence	Patients (n) PRP; Control	Male (n) PRP; Control	Mean age (y) PRP; Control	Repair Type	Tears <3 cm (n) PRP; Control	Tears >3 cm (n) PRP; Control	Minimum Follow-up (mo)		Imaging Modality	Outcome measures
									Clinical	Imaging		
Márquez	2011	II	28 (14; 14)	8 (NR; NR)	65 (NR; NR)	Single-row	0	28 (14; 14)	12	12	MRA	Constant score,
Randelli	2011	I	45 (22; 23)	21 (8; 13)	(61.6; 59.5)	Single-row	29 (14; 15)	16 (8; 8)	12	12	MRI, MRA, US	Constant score, UCLA,SST, tendon integrity
Castricini	2011	I	88 (43; 45)	40 (17; 23)	(55.2; 55.2)	Double-row	88 (43; 45)	0	16	16	MRI	Constant score, tendon integrity
Rodeo	2012	II	67 (35; 32)	44 (23; 21)	(58.9; 57.2)	Double-row	59 (30; 29)	20 (10; 10)	12	3	US	ASES, L'Insalata,
Gumina	2012	I	76 (39; 37)	41 (20; 21)	61(60; 63)	Single-row	0	76 (39; 37)	12	12	MRI	Constant score, SST,
Weber	2013	I	59 (29; 30)	36 (20; 16)	(59.7; 64.5)	Single-row	56 (28; 28)	3 (1; 2)	12	12	MRI	UCLA, ASES, tendon integrity
Ruiz-Moneo	2013	I	63 (32; 31)	25 (14; 11)	(56; 55)	Double-row	36 (18; 18)	27 (14; 13)	12	12	MRA	UCLA,
Jo	2013	I	47 (24; 23)	24 (10; 14)	(64.2; 61.9)	Double-row	0	47 (24; 23)	12	9	MRI, CTA	Constant scale, UCLA,SST, ASES, tendon integrity
Antuna	2013	I	28 (14; 14)	6 (3; 3)	65 (NR; NR)	Single-row	0	28 (14; 14)	12	12	MRA	Constant scale, DASH, VAS
Werthel	2014	II	65 (33; 32)	32 (18; 14)	60 (56; 63)	Double-row	65 (33; 32)	0	12	12	MRI	Constant scale, SST, tendon integrity
Malavolta	2014	I	54 (27; 27)	17 (8; 9)	(55.3; 54.1)	Single-row	54 (27; 27)	0	12	12	MRI	Constant scale, UCLA, tendon integrity
Zumstein	2014	I	20 (10; 10)	10 (6; 4)	(63.6; 64.3)	Double-row	20 (10; 10)	0	3	3	US	Constant scale, SST, VAS
Hak	2015	II	25 (12; 13)	15 (9; 6)	(55; 55)	Single-row	25 (12; 13)	0	1.4	1.4	NR	VAS, DASH, EQ-5D, WORC
Wang	2015	I	60 (30; 30)	28 (11; 17)	(59.8; 58.4)	Double-row	60 (30; 30)	0	3.7	3.7	MRI	VAS, Quick DASH, OSS, SF-12
Jo	2015	I	74 (37; 37)	17 (8; 9)	(60.08; 60.92)	Double-row	0	74 (37; 37)	12	9	MRI	Constant scale, ROM, VAS, CSA

ASES, American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; SST, Simple Shoulder Test; DASH, Disabilities of the Arm, Shoulder, and Hand; UCLA, University of California Los Angeles. VAS, visual analog scale; ROM, range of motion; CTA, computed tomographic arthrography; MRA, magnetic resonance arthrography; MRI, magnetic resonance imaging; NR, not reported; US, ultrasonography. EQ-5D, EuroQol-5 Dimensions; WORC, Western Ontario Rotator Cuff Index, Quick DASH, Quick Disability of the Arm, Shoulder and Hand; OSS, Oxford Shoulder Score; SF-12, Short Form-12. CSA, cross-sectional area.

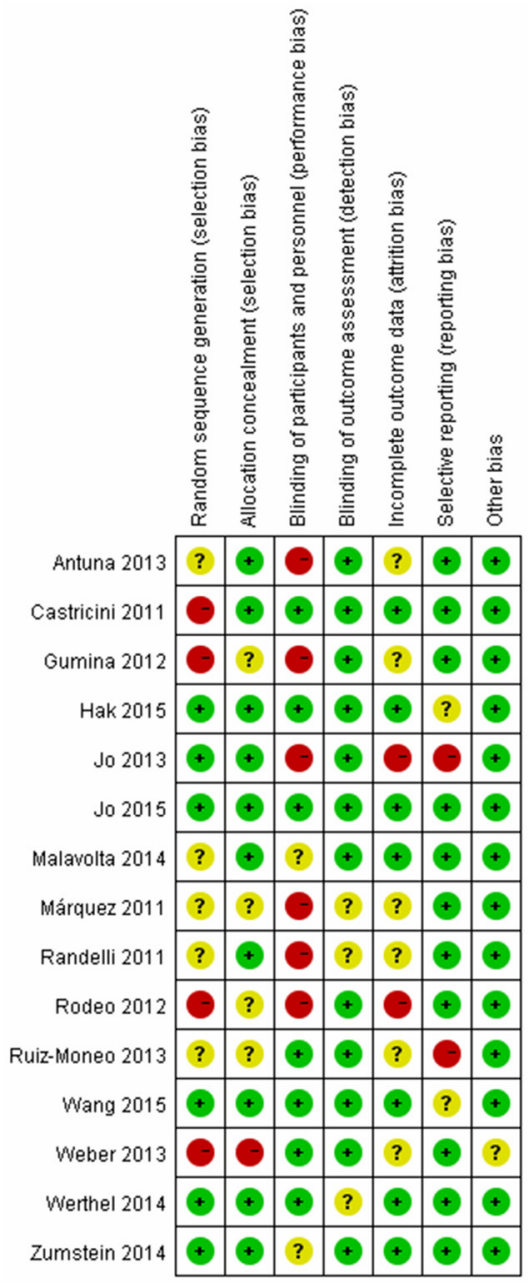

Figure 1. Risk of bias summary: Review authors' judgments of each risk of bias item for each included study.

all studies: Operative time, Constant score, UCLA scale, SER (Kg), ASES score, DASH score, SST scale, VAS scale, CSA (cross-sectional area), SPADI scale, L'Insalata score, MRI rating, Vascularity score, OSS score, Manual muscle testing ratio, EQ-5D score, WORC score, SF-12 Short Form scale (MCS and PCS), Rotator cuff re-tear rate, complications rate, satisfaction rate, complete healing rate, tendon integrity, intact repair rate and radiographic (MRI, MRA and/or US) follow-up times of repaired rotator cuffs. If the studies have reported several different functional outcome results at the different follow-up visit times, the results after different follow-up visits were used for the study. Appropriate recommendations for the use of PRP after arthroscopic rotator cuff tears repair were made according to the pooled measurements of the highest level evidence.

Statistical analysis

The statistical analysis was commonly performed completely in Review Manager (RevMan) [Computer program], version 5.3.5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The relative risks (RRs) for the dichotomous variables were measured using 95% confidence intervals (CIs). Also the weighted mean difference (WMD) was measured using 95% CIs for all continuous variables. *P* values<0.05 were common considered statistically significant, then the 95% confidence intervals (CIs) were also reported. Statistical heterogeneity between all studies was evaluated using the Q-statistic and quantified using the I^2 statistic. Fixed-effects models and random-effects models were commonly used to obtain final summary RRs or WMDs. If the statistic value of Q or I^2 was significant, then the random-effects model was used. Otherwise, the fixed-effects model was used. Funnel plots and Egger's test for meta-analysis (with P<0.05 considered statistically significant) were created to visually evaluate for the presence of publication bias. The sensitivity analysis was also conducted by software, each randomized controlled trials (RCTs) were excluded respectively to determine the stability of all combined RRs or WMDs.

Results

Literature search

An initial 1,122 articles were identified. After 1,017 duplicates and unrelated articles were excluded, 105 articles were assessed for detailed evaluation. A careful abstract review of all titles excluded 90 articles that did not pertain to the topic of interest, which left 15 studies for further full article review. Therefore, 15 studies met our selection criteria and were completely suitable for our meta-analysis [14,

16-29]. All studies were prospective randomized control trials. A total of 799 patients (401 With PRP and 398 Without PRP) were enrolled in our meta-analysis. The key characteristics of all included studies were summarized in **Table 1**. All studies involved the patients with full thickness rotator cuff tearsand arthroscopic rotator cuff repair were followed-up for at least 1 months. Fifteen level I or II RCT studies from 2011 to 2015 that compared PRP with placebo for the treatment of arthroscopic rotator cuff repair prospectively and randomly were identified [14, 16-29]. There was complete agreement (100%) between the two independent reviewers for the entire final data extraction. **Figure 1** summarizes the methodological quality of all included studies. All studies were RCTs, along with a high level for methodological quality. Therefore, the methodological bias for this study was very low.

Main analysis

Table 2 summarizes all clinical outcomes of this meta-analysis. No significant differences were found between PRP group and Placebo group forfinal efficacy and clinical outcomes when all of the patients were pooled into the meta-analysis: operative time (minutes) (WMD, 21.85, 95% CI, -3.53 to 47.23; P=0.09), constant scale (24 months) (WMD, 2.49, 95% CI, -1.58 to 6.57; P=0.23), UCLA score (24 months) (WMD, 0.92, 95% CI, -1.29 to 3.13; P=0.41), SER (Kg) (24 months) (WMD, 0.30, 95% CI, -0.94 to 1.54; P=0.63), ASES score (12 months) (WMD, 0.05, 95% CI, -4.46 to 4.57; P=0.98), DASH score (12 months) (WMD, -3.61, 95% CI, -10.81 to 3.59; P=0.33), SST score (24 months) (WMD, 0.40, 95% CI, -0.28 to 1.08; P=0.25), VAS scale (24 months) (WMD, -0.19, 95% CI, -1.30 to 0.92; P=0.74), CSA (cross-sectional area) (12 months) (WMD, 44.86, 95% CI, -5.22 to 94.94; P=0.08), SPADI scale (12 months) (WMD, -3.22, 95% CI, -7.89 to 1.46; P=0.18), L'Insalata score (12 months) (WMD, -3.72, 95% CI, -8.65 to 1.21; P=0.14), MRI rating (16 weeks) (WMD, -0.30, 95% CI, -0.91 to 0.31; P=0.34), OSS score (16 weeks) (WMD, -2.20, 95% CI, -5.36 to 0.96; P=0.17), Manual muscle testing ratio (12 months) (WMD, 0.01, 95% CI, -0.24 to 0.26; P=0.94), EQ-5D score (6 weeks) (WMD, 0.05, 95% CI, -0.10 to 0.21; P=0.52), WORC score (6 weeks) (WMD, 0.00, 95% CI, -15.45 to 15.45; P=1.00), SF-12 Short Form (MCS) (16 weeks) (WMD, -1.36, 95% CI, -6.17 to 3.45; P=0.58) and SF-12 Short Form (PCS) (16 weeks) (WMD, -1.30, 95% CI, -5.03 to 2.43; P=0.49).

There was no significant difference observed in post-operative complications between PRP group and Placebo group, including general complications (RR, 1.35, 95% CI, 0.36 to 5.14; P=0.66). The fixed-effects model was used because no significant heterogeneity in post-operative complications was observed between the studies.

The RR of Small and medium rotator cuff re-tear rate was 66% lower in PRP group compared to Placebo group (RR, 0.34, 95% CI, 0.12 to 0.94; P=0.04). The RR of Large and massive rotator cuff re-tear rate was not significant, and so was the overall rotator cuff re-tear rate. No significant difference was observed for satisfaction rate (RR, 1.09, 95% CI, 0.99 to 1.21; P=0.09) and complete healing rate (RR, 1.40, 95% CI, 0.96 to 2.04; P=0.08).

No significant difference was finally observed between PRP group and Placebo group for repair integrity or intact repair rate when all of the patients were pooled into our meta-analysis. If any significant heterogeneity was observed, the random-effects model was used because no significant clinical heterogeneity was observed between include RCT studies.

There were also no significant differences for most final outcome measures in PRP group.

Publication bias

Funnel plots and Egger's test *P* value demonstrated no significant evidence of publication bias.

Discussion

This meta-analysis included Level I and II studies focus on final efficacy of PRP use for arthroscopic rotator cuff repairs. A lower re-tear rate was found in patients using PRP among small and medium-sized tears compared with placebo at final follow-up postoperatively, although there was no significant difference in clinical outcomes. The main findings of our study were that PRP does not increase the tend on healing rate or improve the shoulder function scores in arthroscopic full-thickness rotator cuff repair.

Table 2. Meta-analysis of the outcomes of interest

Outcomes of interest	Follow-up time	Number of studies	Participants (n)	Overall effect			Heterogeneity	
				Statistical method	Effect estimate	*P*-value	I^2 %	*P*-value
Constant Scale	Pre-op	8	482	MD (Fixed, 95% CI)	**2.87 [1.55, 4.20]**	<0.0001	40	0.11
	3 mo	3	173	MD (Fixed, 95% CI)	**4.13 [0.14, 8.12]**	0.04	30	0.24
	6 mo	3	173	MD (Fixed, 95% CI)	3.23 [-0.89, 7.35]	0.12	0	0.61
	12 mo	7	390	MD (Fixed, 95% CI)	**2.82 [1.09, 4.56]**	0.001	25	0.24
	16 mo	1	88	MD (Fixed, 95% CI)	0.00 [-3.22, 3.22]	1.00	NA	NA
	24 mo	2	99	MD (Fixed, 95% CI)	2.49 [-1.58, 6.57]	0.23	0	0.37
UCLA	Pre-op	5	284	MD (Fixed, 95% CI)	0.43 [-0.67, 1.52]	0.44	20	0.29
	3 mo	3	173	MD (Fixed, 95% CI)	**2.41 [0.85, 3.97]**	0.002	0	0.90
	6 mo	3	173	MD (Fixed, 95% CI)	1.40 [-0.21, 3.01]	0.09	0	0.98
	12 mo	6	343	MD (Random, 95% CI)	0.70 [-0.68, 2.07]	0.32	47	0.09
	24 mo	2	99	MD (Random, 95% CI)	0.92 [-1.29, 3.13]	0.41	58	0.12
SER (Kg)	Pre-op	2	93	MD (Fixed, 95% CI)	-0.22 [-0.99, 0.55]	0.57	0	0.65
	3 mo	1	45	MD (Fixed, 95% CI)	**0.90 [0.05, 1.75]**	0.04	NA	NA
	6 mo	1	45	MD (Fixed, 95% CI)	0.60 [-0.43, 1.63]	0.25	NA	NA
	12 mo	2	93	MD (Fixed, 95% CI)	0.01 [-0.71, 0.72]	0.99	0	0.38
	24 mo	1	45	MD (Fixed, 95% CI)	0.30 [-0.94, 1.54]	0.63	NA	NA
ASES	Pre-op	3	188	MD (Fixed, 95% CI)	2.12 [-3.60, 7.84]	0.47	42	0.18
	6 wk	1	58	MD (Fixed, 95% CI)	-6.82 [-15.57, 1.93]	0.13	NA	NA
	3 mo	2	129	MD (Fixed, 95% CI)	-0.92 [-7.21, 5.36]	0.77	0	0.49
	6 mo	1	74	MD (Fixed, 95% CI)	5.06 [-3.77, 13.89]	0.26	NA	NA
	12 mo	4	222	MD (Random, 95% CI)	0.05 [-4.46, 4.57]	0.98	54	0.09
DASH	Pre-op	3	133	MD (Fixed, 95% CI)	5.98 [-0.63, 12.6]	0.08	0	0.96
	2 wk	1	25	MD (Fixed, 95% CI)	-10.30 [-26.9, 6.3]	0.22	NA	NA
	1 mo	1	25	MD (Fixed, 95% CI)	1.30 [-11.55, 14.15]	0.84	NA	NA
	6 wk	2	84	MD (Fixed, 95% CI)	-1.55 [-9.06, 5.96]	0.69	0	0.70
	12 wk	1	60	MD (Fixed, 95% CI)	-3.19 [-12.48, 6.1]	0.50	NA	NA
	16 wk	1	60	MD (Fixed, 95% CI)	5.35 [-1.72, 12.42]	0.14	NA	NA
	12 mo	1	48	MD (Fixed, 95% CI)	-3.61 [-10.81, 3.59]	0.33	NA	NA
SST	Pre-op	5	312	MD (Fixed, 95% CI)	0.33 [-0.03, 0.70]	0.08	0	0.54
	3 mo	2	119	MD (Random, 95% CI)	0.84 [-0.92, 2.60]	0.35	73	0.05
	6 mo	2	119	MD (Fixed, 95% CI)	0.48 [-0.35, 1.31]	0.26	3	0.31
	12 mo	5	308	MD (Fixed, 95% CI)	0.29 [-0.02, 0.60]	0.07	47	0.11
	24 mo	1	45	MD (Fixed, 95% CI)	0.40 [-0.28, 1.08]	0.25	NA	NA
VAS	Pre-op	6	305	MD (Random 95% CI)	-0.00 [-0.81, 0.81]	0.99	63	0.02
	1 dy	1	51	MD (Fixed, 95% CI)	-0.29 [-1.81, 1.23]	0.71	NA	NA
	3 dy	1	45	MD (Fixed, 95% CI)	**-2.30 [-4.06, -0.54]**	0.01	NA	NA
	1 wk	2	96	MD (Fixed, 95% CI)	**-1.12 [-2.21, -0.03]**	0.04	43	0.19
	2 wk	2	70	MD (Fixed, 95% CI)	-0.97 [-2.20, 0.26]	0.12	49	0.16
	1 mo	5	243	MD (Random, 95% CI)	-0.08 [-1.07, 0.91]	0.87	76	0.002
	3 mo	4	212	MD (Fixed, 95% CI)	0.15 [-0.44, 0.74]	0.61	0	0.88
	6 mo	3	188	MD (Fixed, 95% CI)	0.01 [-0.54, 0.56]	0.96	0	0.46
	12 mo	2	128	MD (Fixed, 95% CI)	-0.49 [-1.06, 0.08]	0.09	0	0.71
	24 mo	1	54	MD (Fixed, 95% CI)	-0.19 [-1.30, 0.92]	0.74	NA	NA
CSA (cross-sectional area)	Pre-op	2	93	MD (Fixed, 95% CI)	13.46 [-32.91, 59.84]	0.57	0	0.69
	1 dy	2	93	MD (Fixed, 95% CI)	1.64 [-44.35, 47.64]	0.94	0	0.73
	12 mo	2	93	MD (Fixed, 95% CI)	44.86 [-5.22, 94.94]	0.08	0	0.69
SPADI	Pre-op	2	122	MD (Random, 95% CI)	-0.88 [-20.04, 18.27]	0.93	79	0.03
	3 mo	1	74	MD (Fixed, 95% CI)	1.04 [-8.15, 10.23]	0.82	NA	NA
	6 mo	1	74	MD (Fixed, 95% CI)	-6.38 [-15.38, 2.62]	0.16	NA	NA
	12 mo	2	122	MD (Fixed, 95% CI)	-3.22 [-7.89, 1.46]	0.18	0	0.78
L'Insalata	Pre-op	1	60	MD (Fixed, 95% CI)	-0.02 [-6.99, 6.95]	1.00	NA	NA
	6 wk	1	52	MD (Fixed, 95% CI)	-6.75 [-14.19, 0.69]	0.08	NA	NA
	3 mo	1	52	MD (Fixed, 95% CI)	-0.69 [-8.28, 6.90]	0.86	NA	NA
	12 mo	1	34	MD (Fixed, 95% CI)	-3.72 [-8.65, 1.21]	0.14	NA	NA

MRI rating	16 wk	1	40	MD (Fixed, 95% CI)	-0.30 [-0.91, 0.31]	0.34	NA	NA
Vascularity score								
Total	6 wk	1	20	MD (Fixed, 95% CI)	**4.00 [0.89, 7.11]**	0.01	NA	NA
	3 mo	1	20	MD (Fixed, 95% CI)	**2.60 [0.27, 4.93]**	0.03	NA	NA
Lateral	6 wk	1	20	MD (Fixed, 95% CI)	**2.00 [0.62, 3.38]**	0.004	NA	NA
	3 mo	1	20	MD (Fixed, 95% CI)	0.80 [-0.78, 2.38]	0.32	NA	NA
Intermediate	6 wk	1	20	MD (Fixed, 95% CI)	**1.80 [0.16, 3.44]**	0.03	NA	NA
	3 mo	1	20	MD (Fixed, 95% CI)	**0.80 [0.05, 1.55]**	0.04	NA	NA
Medial	6 wk	1	20	MD (Fixed, 95% CI)	0.30 [-1.28, 1.88]	0.71	NA	NA
	3 mo	1	20	MD (Fixed, 95% CI)	1.10 [-0.04, 2.24]	0.06	NA	NA
OSS	Pre-op	1	60	MD (Fixed, 95% CI)	-3.05 [-6.77, 0.67]	0.11	NA	NA
	6 wk	1	60	MD (Fixed, 95% CI)	2.09 [-2.08, 6.26]	0.33	NA	NA
	12 wk	1	60	MD (Fixed, 95% CI)	0.85 [-3.19, 4.89]	0.68	NA	NA
	16 wk	1	60	MD (Fixed, 95% CI)	-2.20 [-5.36, 0.96]	0.17	NA	NA
Manual muscle testing ratio	Pre-op	1	56	MD (Fixed, 95% CI)	0.05 [-0.16, 0.26]	0.64	NA	NA
	3 mo	1	61	MD (Fixed, 95% CI)	0.10 [-0.02, 0.22]	0.10	NA	NA
	12 mo	1	40	MD (Fixed, 95% CI)	0.01 [-0.24, 0.26]	0.94	NA	NA
EQ-5D Score	Pre-op	1	25	MD (Fixed, 95% CI)	-0.06 [-0.23, 0.11]	0.50	NA	NA
	2 wk	1	25	MD (Fixed, 95% CI)	0.00 [-0.19, 0.19]	1.00	NA	NA
	4 wk	1	25	MD (Fixed, 95% CI)	0.06 [-0.09, 0.20]	0.45	NA	NA
	6 wk	1	24	MD (Fixed, 95% CI)	0.05 [-0.10, 0.21]	0.52	NA	NA
WORC	Pre-op	1	25	MD (Fixed, 95% CI)	-11.20 [-23.47, 1.07]	0.07	NA	NA
	2 wk	1	25	MD (Fixed, 95% CI)	-4.90 [-16.59, 6.79]	0.41	NA	NA
	4 wk	1	25	MD (Fixed, 95% CI)	-9.40 [-23.04, 4.24]	0.18	NA	NA
	6 wk	1	24	MD (Fixed, 95% CI)	0.00 [-15.45, 15.45]	1.00	NA	NA
SF-12 Short Form								
MCS	Pre-op	1	60	MD (Fixed, 95% CI)	1.69 [-4.59, 7.97]	0.60	NA	NA
	6 wk	1	60	MD (Fixed, 95% CI)	0.18 [-6.55, 6.91]	0.96	NA	NA
	12 wk	1	60	MD (Fixed, 95% CI)	-0.72 [-6.41, 4.97]	0.80	NA	NA
	16 wk	1	60	MD (Fixed, 95% CI)	-1.36 [-6.17, 3.45]	0.58	NA	NA
PCS	Pre-op	1	60	MD (Fixed, 95% CI)	-2.75 [-6.90, 1.40]	0.19	NA	NA
	6 wk	1	60	MD (Fixed, 95% CI)	1.33 [-2.02,4. 68]	0.44	NA	NA
	12 wk	1	60	MD (Fixed, 95% CI)	-0.35 [-3.89, 3.19]	0.85	NA	NA
	16 wk	1	60	MD (Fixed, 95% CI)	-1.30 [-5.03, 2.43]	0.49	NA	NA
Operative time (min)	Op	2	79	MD (Random, 95% CI)	21.85 [-3.53, 47.23]	0.09	85	0.009
Rotator cuff retear rate	Final	11	597	RR (Random, 95% CI)	0.65 [0.40, 1.06]	0.08	41	0.08
Small- and medium	Final	4	267	RR (Fixed, 95% CI)	**0.34 [0.12, 0.94]**	0.04	0	0.96
Large- and massive	Final	5	233	RR (Random, 95% CI)	0.41 [0.12, 1.40]	0.16	73	0.01
Complications	Final	9	408	RR (Fixed, 95% CI)	1.35 [0.36, 5.14]	0.66	0	0.49
Satisfaction rate	Final	7	353	RR (Fixed, 95% CI)	1.09 [0.99, 1.21]	0.09	0	0.46
Complete healing rate	Final	5	257	RR (Fixed, 95% CI)	1.40 [0.96, 2.04]	0.08	0	0.79
Repair integrity								
Intact	6 wk	1	70	RR (Fixed, 95% CI)	0.99 [0.80, 1.22]	0.91	NA	NA
	3 mo	4	201	RR (Fixed, 95% CI)	1.08 [0.91, 1.28]	0.39	48	0.12
	6 mo	1	54	RR (Fixed, 95% CI)	1.14 [0.92, 1.40]	0.23	NA	NA
	12 mo	3	145	RR (Fixed, 95% CI)	1.21 [0.97, 1.52]	0.09	0	0.43
Contrast leak	3 mo	2	80	RR (Fixed, 95% CI)	0.90 [0.41, 1.98]	0.79	0	0.66
	12 mo	2	91	RR (Fixed, 95% CI)	0.69 [0.33, 1.48]	0.34	0	0.44
Re-tear	3 mo	3	134	RR (Fixed, 95% CI)	0.56 [0.25, 1.23]	0.15	30	0.24
	6 mo	1	54	RR (Fixed, 95% CI)	0.40 [0.08, 1.89]	0.25	NA	NA
	12 mo	3	145	RR (Random, 95% CI)	0.55 [0.12, 2.50]	0.44	71	0.03
Intact repair rate								
Double-row	6 wk	1	37	RR (Fixed, 95% CI)	0.85 [0.66, 1.09]	0.20	NA	NA
	12 wk	3	116	RR (Random, 95% CI)	0.96 [0.56, 1.67]	0.90	74	0.02
Single-row	6 wk	1	25	RR (Fixed, 95% CI)	0.90 [0.67, 1.22]	0.50	NA	NA
	12 wk	2	75	RR (Random, 95% CI)	1.09 [0.79, 1.51]	0.61	54	0.14

Notes: The bold numbers mean that the effect estimate values for the contrast models are significant.models are significant. Abbreviations: MD, weighted mean difference; RR, relative risk; NA, not applicable; CI, confidence interval.

Several clinical trials investigated the clinical outcomes of arthroscopic rotator cuff repair surgery with platelet-rich plasma, and these trials showed mixed outcomes [14, 16-23]. Some animal studies [30, 31] have shown beneficial effects only on the initial stage among rotator cuff tendon-to-bone healing progress with the application of PRP. However, compared with placebo treatment, our meta-analysis found no superiority in clinical outcomes with PRP application. From our meta-analysis data, although the healing rate in small and medium-sized full-thickness rotator tears in PRP group was higher, clinical outcomes showed no statistically significant differences. We found no evidence for an increase or decrease inassociated complications with the use of PRP.

One of the most difficult problems with PRP use is that there are no standard preparation protocols, and different concentration of growth factors exist in various PRP products. Irrigation during surgery and swelling after surgery may also reduce the effectiveness of PRP. For further research on PRP, the demand for its clinical applications will also increase. PRP is a whole-blood fraction that can be simply isolated with a simple device, which suggests that the preparation is less expensive than other biological factors such as MSCs.

The limitations of the our study are: first, we included all Level I and II evidence studies to enhance the power of our meta-analysis, which may have induced reporting bias to our results; and second, the clinical heterogeneity of all included studies was bit high. Different studies used different surgical techniques (single-row and double-row technology), and tear size varied from small to large. Third, different PRP products and arbitrary volume of PRP were used among studies. Finally, although we have included 15 studies, the included studies whose patient number matched available outcomes with regard to the follow-up time point were small. Hence, overall sample size seems to not have adequate power to detect the smaller differences.

In the near future, multi-center prospective randomized control trials with more patients and various subgroups according to repair technology and tear size are needed. Although this study has many limitations, our meta-analysis is still powerful enough to guide present clinical work.

Conclusion

Our meta-analysis does not support the application of platelet-rich plasma in arthroscopic repair for full-thickness rotator cuff tears better than repairs without PRP because of the similar re-tear rates and final clinical outcomes. However, we observed a decrease in the re-tears rate among patients who treated with PRP in the subgroup of small and medium-sized rotator cuff tears.

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Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: W.Y.X and R.G.L and J.S.C; Analyzed the data: J.S and Q.C.M and X.B.C; Wrote the paper: P.C.L and J.X.S.

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References

[1] Edwards SL, Lynch TS, Saltzman MD, Terry MA, Nuber GW. Biologic and pharmacologic augmentation of rotator cuff repairs. J Am Acad Orthop Surg 2011; 19: 583-9.

[2] Colvin AC, Egorova N, Harrison AK, Moskowitz A, Flatow EL. National trends in rotator cuff repair. J Bone Joint Surg Am 2012; 94: 227-33.

[3] Cole BJ, McCarty LR, Kang RW, Alford W, Lewis PB, Hayden JK. Arthroscopic rotator cuff repair: prospective functional outcome and repair integrity at minimum 2-year follow-up. J Shoulder Elbow Surg 2007; 16: 579-85.

[4] Millett PJ, Warth RJ, Dornan GJ, Lee JT, Spiegl UJ. Clinical and structural outcomes after arthroscopic single-row versus double-row rotator cuff repair: a systematic review and meta-analysis of level I randomized clinical trials. J Shoulder Elbow Surg 2014; 23: 586-97.

[5] Sugaya H, Maeda K, Matsuki K, Moriishi J. Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair. A

prospective outcome study. J Bone Joint Surg Am 2007; 89: 953-60.
[6] Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am 2004; 86-A: 219-24.
[7] Gulotta LV, Rodeo SA. Growth factors for rotator cuff repair. Clin Sports Med 2009; 28: 13-23.
[8] Pacifici L, Casella F, Maggiore C. [Platelet rich plasma (PRP): potentialities and techniques of extraction]. Minerva Stomatol 2002; 51: 341-50.
[9] Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg 2009; 17: 602-8.
[10] Mei-Dan O, Carmont MR. The role of platelet-rich plasma in rotator cuff repair. Sports Med Arthrosc 2011; 19: 244-50.
[11] Bosch G, van Schie HT, de Groot MW, Cadby JA, van de Lest CH, Barneveld A, van Weeren PR. Effects of platelet-rich plasma on the quality of repair of mechanically induced core lesions in equine superficial digital flexor tendons: A placebo-controlled experimental study. J Orthop Res 2010; 28: 211-7.
[12] de Mos M, van der Windt AE, Jahr H, van Schie HT, Weinans H, Verhaar JA, van Osch GJ. Can platelet-rich plasma enhance tendon repair? A cell culture study. Am J Sports Med 2008; 36: 1171-8.
[13] McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. J Orthop Res 2009; 27: 1033-42.
[14] Márquez JS, Díez JM, Barco R, Antuña S. Functional results after arthroscopic repair of massive rotator cuff tears; influence of the application platelet-rich plasma combined with fibrin. Revista Española de Cirugía Ortopédica y Traumatología (English Edition) 2011; 55: 282-7.
[15] Jo CH, Kim JE, Yoon KS, Lee JH, Kang SB, Lee JH, Han HS, Rhee SH, Shin S. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. Am J Sports Med 2011; 39: 2082-90.
[16] Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg 2011; 20: 518-28.
[17] Castricini R, Longo UG, De Benedetto M, Panfoli N, Pirani P, Zini R, Maffulli N, Denaro V. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med 2011; 39: 258-65.
[18] Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. Am J Sports Med 2012; 40: 1234-41.
[19] Gumina S, Campagna V, Ferrazza G, Giannicola G, Fratalocchi F, Milani A, Postacchini F. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. J Bone Joint Surg Am 2012; 94: 1345-52.
[20] Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. Am J Sports Med 2013; 41: 263-70.
[21] Ruiz-Moneo P, Molano-Munoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: a randomized, double-blind, controlled clinical trial. Arthroscopy 2013; 29: 2-9.
[22] Jo CH, Shin JS, Lee YG, Shin WH, Kim H, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single-blind, parallel-group trial. Am J Sports Med 2013; 41: 2240-8.
[23] Antuna S, Barco R, Martinez DJ, Sanchez MJ. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: a prospective randomized pilot clinical trial. Acta Orthop belg 2013; 79: 25-30.
[24] Malavolta EA, Gracitelli ME, Ferreira NA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. Am J Sports Med 2014; 42: 2446-54.
[25] Zumstein MA, Rumian A, Lesbats V, Schaer M, Boileau P. Increased vascularization during early healing after biologic augmentation in repair of chronic rotator cuff tears using autologous leukocyte- and platelet-rich fibrin (L-PRF): a prospective randomized controlled pilot trial. J Shoulder Elbow Surg 2014; 23: 3-12.
[26] Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: a randomized controlled trial. Am J Sports Med 2015; 43: 2102-10.
[27] Wang A, McCann P, Colliver J, Koh E, Ackland T, Joss B, Zheng M, Breidahl B. Do postoperative platelet-rich plasma injections accelerate early tendon healing and functional recovery after arthroscopic supraspinatus repair? A randomized controlled trial. Am J Sports Med 2015; 43: 1430-7.

[28] Hak A, Rajaratnam K, Ayeni OR, Moro J, Peterson D, Sprague S, Bhandari M. A Double-Blinded Placebo Randomized Controlled Trial Evaluating Short-term Efficacy of Platelet-Rich Plasma in Reducing Postoperative Pain After Arthroscopic Rotator Cuff Repair: A Pilot Study. Sports Health 2015; 7: 58-66.

[29] Werthel JD, Pelissier A, Massin P, Boyer P, Valenti P. Arthroscopic double row cuff repair with suture-bridging and autologous conditioned plasma injection: Functional and structural results. Int J Shoulder Surg 2014; 8: 101-6.

[30] Beck J, Evans D, Tonino PM, Yong S, Callaci JJ. The biomechanical and histologic effects of platelet-rich plasma on rat rotator cuff repairs. Am J Sports Med 2012; 40: 2037-44.

[31] Hapa O, Cakici H, Kukner A, Aygun H, Sarkalan N, Baysal G. Effect of platelet-rich plasma on tendon-to-bone healing after rotator cuff repair in rats: an in vivo experimental study. Acta Orthop Traumatol Turc 2012; 46: 301-7.