Clinical Sports Medicine Update

The Efficacy of Platelet-Rich Plasma and Platelet-Rich Fibrin in Arthroscopic Rotator Cuff Repair

A Meta-analysis of Randomized Controlled Trials

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Background: Basic science studies suggest that platelet-rich therapies have a positive effect on tendon repair. However, the clinical evidence is conflicted on whether this translates to increased tendon healing and improved functional outcomes.

Purpose: To perform a systematic review of randomized controlled trials (RCTs) in the literature to ascertain whether platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) improved patient outcomes in arthroscopic rotator cuff repair.

Study Design: Meta-analysis.

Methods: Two independent reviewers performed the literature search based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with a third author resolving any discrepancies. RCTs comparing PRP or PRF to a control in rotator cuff repair were included. Quality of evidence was assessed using the Jadad score. Clinical outcomes were compared using the risk ratio for dichotomous variables and the mean difference for continuous variables. A P value $<.05$ was deemed statistically significant.

Results: Eighteen RCTs with 1147 patients were included in this review. PRP resulted in significantly decreased rates of incomplete tendon healing for all tears combined (17.2% vs 30.5%, respectively; $P < .05$), incomplete tendon healing in small-medium tears (22.4% vs 38.3%, respectively; $P < .05$), and incomplete tendon healing in medium-large tears (12.3% vs 30.5%, respectively; $P < .05$) compared to the control. There was a significant result in favor of PRP for the Constant score (85.6 vs 83.1, respectively; $P < .05$) and the visual analog scale score for pain at 30 days postoperatively (2.9 vs 4.3, respectively; $P < .05$) and at final follow-up (1.2 vs 1.4, respectively; $P < .05$) compared to the control. PRF did not result in a significantly decreased rate of incomplete tendon healing for all tears combined (23.0% vs 24.6%, respectively; $P = .74$) or an improved Constant score (80.8 vs 79.8, respectively; $P = .27$) compared to the control. PRF resulted in a significantly longer operation time (99.1 vs 83.3 minutes, respectively; $P < .05$) compared to the control.

Conclusion: The current evidence indicates that the use of PRP in rotator cuff repair results in improved healing rates, pain levels, and functional outcomes. In contrast, PRF has been shown to have no benefit in improving tendon healing rates or functional outcomes.

Keywords: biologic; platelet-rich plasma; rotator cuff; meta-analysis; systematic review

A rotator cuff tear is a common injury, with 250,000 to 300,000 rotator cuff repairs being performed annually in the United States.[45] Consequently, arthroscopic rotator cuff repair has become a primary research focus for orthopaedic surgeons to enhance the current treatment paradigm to improve patient outcomes and quality of life. Biologics such as platelet-rich therapies (PRTs) have become increasingly popular in recent years as an adjuvant to surgery.[34,48]

PRTs can be broadly subgrouped into platelet-rich plasma (PRP) or platelet-rich fibrin (PRF), with leukocyte-poor and leukocyte-rich versions of either.[13] The growth factors in PRTs can influence healing and reduce inflammation

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by augmented cellular migration, cellular proliferation, angiogenesis, and matrix deposition, which make them a potentially viable option in rotator cuff repair.[2,47] Several basic science studies have shown PRTs to have a potential positive effect on tendon repair through increased tenocyte proliferation, platelet-derived growth factor (PDGF), and transforming growth factor (TGF).[2] In recent years, the clinical application of PRP and PRF in rotator cuff repair has increased, leading to several randomized controlled trials (RCTs) evaluating PRP compared with a control.[17] Additionally, multiple other trials are currently being conducted on the use of biologic augmentation for rotator cuff repair that have not yet been published and can be found on clinicaltrials.gov.

The American Academy of Orthopaedic Surgeons has no recommendations for PRTs for rotator cuff repair. Several systematic reviews of RCTs have shown that PRP and PRF improve tendon healing in small-medium tears but not in larger sized tears, but these have been limited by combining PRP and PRF and the low number of included studies. As a result of this, they may be underpowered and have recommended that further studies are necessary.[6,16,31,41,43,49,51] However, several new RCTs have been published comparing PRP or PRF to a control, which warrants an updated systematic review.[‖] Therefore, the purpose of this study was to perform a systematic review of RCTs in the literature to ascertain whether PRP or PRF improved patient outcomes in arthroscopic rotator cuff repair. PRP and PRF are both processed from autologous blood at the time of surgery or before, but they differ in their preparation methods.[13] PRP is collected with anticoagulant and is immediately processed, while PRF is collected immediately without anticoagulant so that it forms a fibrin-rich clot that has to be sutured to the bone-tendon interface.[13] It was hypothesized that PRP and PRF would lead to improved patient outcomes compared with a control.

METHODS

Study Selection

Two independent reviewers performed the literature search based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and reviewed the search results, with a third author arbitrating any discrepancies.[32] The title and abstract were reviewed for all search results, and potentially eligible studies received a full-text review. In addition, the reference lists of all included studies and all literature reviews found in the search results were manually screened for additional articles that met the inclusion criteria.

Search Strategy

The following search terms were used in MEDLINE, Embase, ClinicalTrials.gov, and The Cochrane Library databases on March 24, 2017: (rotator cuff OR rotator cuff tear OR rotator cuff repair OR arthroscopic rotator cuff repair OR shoulder arthroscopy) AND (PRP OR platelet-rich plasma OR PRF OR platelet-rich fibrin OR platelet OR platelet-rich). No time limit was given to the publication date.

Eligibility Criteria

The inclusion criteria were (1) RCTs or quasi-RCTs comparing PRP or PRF and a control in arthroscopic rotator cuff repair, (2) published in a peer-reviewed journal, (3) published in English, and (4) full text of studies available. The exclusion criteria were (1) nonrandomized studies, (2) retrospective studies, (3) review studies, and (4) basic science studies.

Data Extraction/Analysis

All relevant information regarding the study characteristics including design, level of evidence, methodological quality of evidence, population, outcome measures, and follow-up time points was collected by 2 independent reviewers using a predetermined data sheet. Studies were defined as leukocyte-poor PRP/PRF or leukocyte-rich PRP by the manufacturer's specifications and whether they had more or fewer leukocytes than autologous blood. The level of evidence was evaluated based on the criteria of the Oxford Centre for Evidence-Based Medicine. The risk of bias was assessed for RCTs using the Jadad 5-point scale. Studies with a Jadad score of >3 were considered to have a low risk of bias.[24]

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan for Macintosh Version 5.3; The Cochrane Collaboration). Primary results were analyzed to compare PRP versus a control and PRF versus a control: (1) incomplete tendon healing rate in tears of all sizes, (2) incomplete tendon healing rate in small-medium (<3 cm) tears, (3) incomplete tendon healing rate in medium-large (>3 cm) tears, (4) patient satisfaction, (5) visual analog scale (VAS) score for pain at day 30, (6) VAS score at final follow-up, (7) Constant score, (8) University of California, Los Angeles (UCLA) score, (9) American Shoulder and Elbow Surgeons (ASES) score, and (10) operation time. Continuous outcomes were calculated and expressed as the mean difference (MD) and dichotomous outcomes as the risk ratio (RR). Heterogeneity between studies was quantified using the I^2 statistic.[21] We chose an I^2 value of $<25\%$ to represent low heterogeneity and an I^2 value of $>75\%$ to indicate high heterogeneity. Fixed-effects models were used. When the range was given instead of an SD, the range was divided by 4 to calculate the SD.[23] Subgroup analysis was performed when there were more than 3 studies using leukocyte-rich PRP or leukocyte-poor PRP; when there was significant heterogeneity in the outcomes reported, this was noted in the text.[39] Results were presented in terms of the MD with a 95% CI. A P value of $<.05$ was considered to be statistically significant.

[‖]References 12, 15, 19, 22, 28, 35, 42, 50, 54.

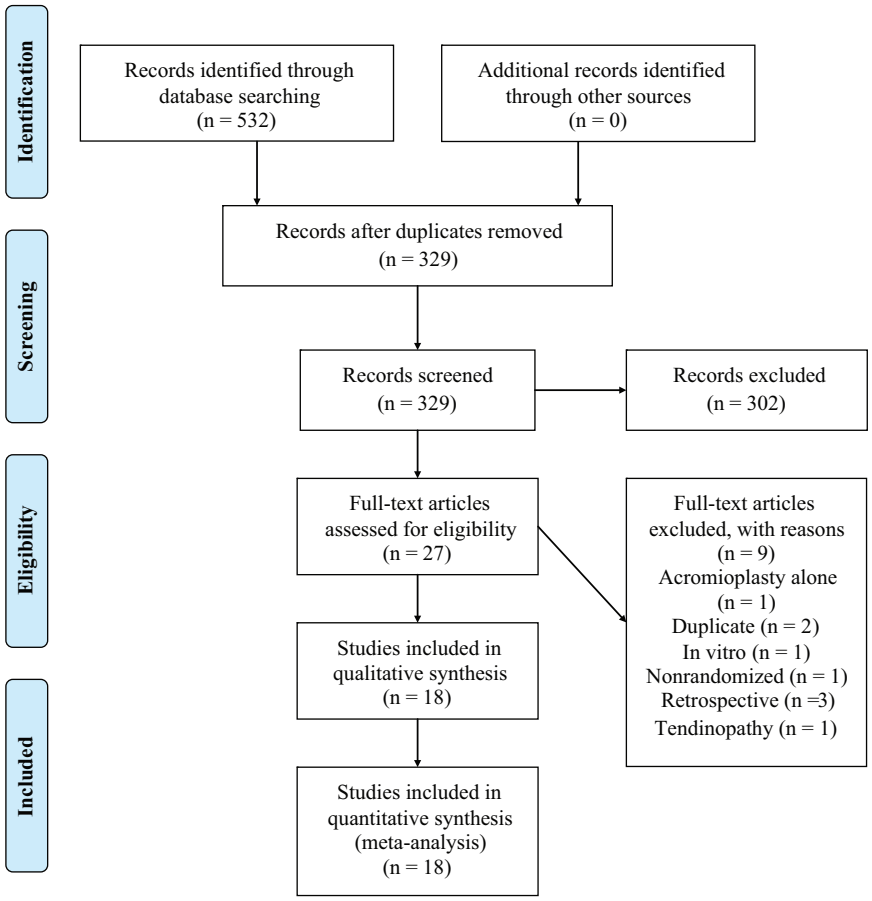

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study selection flow diagram.

RESULTS

Literature Search

The initial literature search identified a total of 532 studies. Once duplicates were removed and the articles were screened for inclusion and exclusion criteria, 27 studies with full texts were assessed for eligibility. Eighteen RCTs or quasi-RCTs with a total of 1162 patients were included in this review (Figure 1). Nine studies were excluded because they evaluated acromioplasty alone, duplicated an included study's results, were in vitro, were nonrandomized, were retrospective, or were about tendinopathy alone.[1,3,5,7,9,25,26,30,53]

Study Characteristics/Patient Demographics

All of the included studies were level 1 or 2 RCTs with a mean Jadad score of 3.8 ± 0.7. Only 3 were considered as having a high risk of bias. There were 12 RCTs comparing 391 patients treated with PRP to 390 patients treated with a control and 6 RCTs comparing 183 patients treated with PRF to 183 patients treated with a control. Tendon healing was assessed by magnetic resonance imaging in 15 studies, ultrasound in 2 studies, a combination of both in 1 study, and not assessed in 1 study at final follow-up. The study characteristics and patient demographics are reported in Table 1.

PRT Injection Characteristics

Twelve studies used PRP, with 9 using leukocyte-poor PRP and 3 studies using leukocyte-rich PRP. There were varying volumes of between 1 and 16 mL of PRP used, and all studies apart from one used PRP intraoperatively. Wang et al[42] used PRP under direct visualization using ultrasound on day 7 and day 14. All studies used PRP at the bone-tendon interface, and 1 study also used it at the intratendon. Six studies used PRF, with 4 using leukocyte-poor PRF and 2 studies using leukocyte-rich PRF. There were varying volumes of between 1 and 9 mL of PRF used, and all studied PRF intraoperatively, as PRF has to be stitched in. All studies used PRP at the bone-tendon interface, and 2 studies also used it in the subacromial space. A control injection of saline was reported in 2 studies, and no control injection was reported in the other 16 studies. The PRT injection characteristics are shown in Table 2.

TABLE 1
Study Characteristics and Patient Demographics[a]

Author (Year)	LOE	Jadad Score	No. of Patients		Age, Mean ± SD, y		Sex, M/F, n		Follow-up, mo
			PRT	C	PRT	C	PRT	C	
Platelet-rich plasma									
D'Ambrosi et al[12] (2016)	1	5	20	20	57.9 ± 8.7	62.0 ± 10.0	9/11	10/10	6
Flury et al[15] (2016)	1	4	60	60	57.8 ± 8.0	58.9 ± 8.2	18/42	20/40	24
Hak et al[19] (2015)	1	4	12	13	55.0 ± 6.3	55.0 ± 6.4	9/3	10/3	1.5
Holtby et al[22] (2016)	1	4	41	41	59.0 ± 8.0	59.0 ± 8.0	21/20	20/21	6
Jo et al[27] (2013)	1	4	24	24	64.2 ± 6.1	61.9 ± 8.4	10/14	14/10	12
Jo et al[28] (2015)	1	4	37	37	61.2 ± 4.9	60.9 ± 7.3	8/29	9/28	12
Malavolta et al[33] (2014)	1	4	27	27	55.3 ± 8.3	54.7 ± 6.6	8/19	9/18	24
Pandey et al[35] (2016)	1	4	52	50	54.8 ± 8.4	54.1 ± 8.3	38/14	36/14	12
Randelli et al[36] (2011)	1	4	26	27	61.6 ± 8.3	59.5 ± 10.7	8/18	13/14	24
Ruiz-Moneo et al[38] (2013)	1	4	32	31	56.0 ± 8.8	55.0 ± 11.0	14/18	11/20	12
Wang et al[42] (2015)	1	4	30	30	59.8 ± 12.3	58.4 ± 9.5	11/19	17/13	4
Zhang et al[50] (2016)	1	2	30	30	57.2 ± 7.4	56.9 ± 6.0	15/15	16/14	12
Platelet-rich fibrin									
Castricini et al[8] (2011)	1	4	43	45	55.5 ± 7.8	55.2 ± 8.0	17/26	23/22	20.2
Gumina et al[18] (2012)	1	2	39	37	60.0 ± 4.4	63.0 ± 5.9	20/19	21/16	13
Rodeo et al[37] (2012)	2	4	40	39	58.9 ± 9.9	57.2 ± 9.4	23/17	21/18	19
Sanchez Marquez et al[39] (2011)	2	3	14	14	65.0 ± 6.3		8/20		12
Weber et al[44] (2013)	1	4	30	30	59.7 ± 8.2	64.5 ± 8.6	20/10	16/14	12
Zumstein et al[54] (2016)	1	5	17	18	65.0 ± 4.0	66.0 ± 4.5	10/7	8/10	12

[a]C, control; F, female; LOE, level of evidence; M, male; PRT, platelet-rich therapy.

TABLE 2
Platelet-Rich Therapy Injection Characteristics[a]

Author (Year)	LR or LP	Volume, mL	Preparation Kit	Platelet Concentration, × 10^3	Activating Agent	Applied Site
Platelet-rich plasma						
D'Ambrosi et al[12] (2016)	LR	16	GPS (Biomet Biologics)	NR	NR	BTI
Flury et al[15] (2016)	LP	4	ACP (Arthrex)	NR	NR	BTI
Hak et al[19] (2015)	LP	6-9	ACP (Arthrex)	NR	NR	BTI + SAS
Holtby et al[22] (2016)	LP	7	SmartPrep 2 (Harvest Technologies)	NR	NR	BTI
Jo et al[27] (2013)	LP	9	COBE Spectra (Terumo BCT)	1000	Calcium gluconate	BTI
Jo et al[28] (2015)	LP	9	COBE Spectra (Terumo BCT)	1000	Calcium gluconate	BTI
Malavolta et al[33] (2014)	LP	10	MCS1 (Haemonetics)	NR	Calcium chloride	BTI
Pandey et al[35] (2016)	LP	8	Heraeus Cryofuge (Thermo Scientific)	474	Calcium chloride	BTI
Randelli et al[36] (2011)	LR	6	GPS (Biomet Biologics)	NR	Calcium chloride	BTI + SAS
Ruiz-Moneo et al[38] (2013)	LP	1	PRGF System 1 (BTI)	600	Calcium chloride	BTI + intratendon
Wang et al[42] (2015)	LP	2 × 2-4	ACP (Arthrex)	470	Calcium chloride	BTI
Zhang et al[50] (2016)	LR	NR	GPS (Biomet Biologics)	NR	Calcium chloride	BTI
Platelet-rich fibrin						
Castricini et al[8] (2011)	LP	NR	NR	NR	Calcium chloride	BTI
Gumina et al[18] (2012)	LR	5.2	RegenKit (RegenLab)	>400	Calcium gluconate	BTI
Rodeo et al[37] (2012)	LP	9	Cascade (MTF)	NR	Calcium chloride	BTI
Sanchez Marquez et al[39] (2011)	LP	7	Vivostat PRF (Vivostat)	NR	NR	BTI
Weber et al[44] (2013)	LP	1	Cascade (MTF)	NR	Calcium	BTI
Zumstein et al[54] (2016)	LR	NR	NR	NR	NR	BTI

[a]BTI, bone-tendon interface; LP, leukocyte-poor; LR, leukocyte-rich; NR, not reported; SAS, subacromial space.

Clinical Outcomes in PRP

The forest plots can be found in the Appendix (available in the online version of this article).

Tendon Healing Rate. Tendon healing was reported in 11 studies, with 355 patients treated with PRP and 351 with a control. With PRP, 17.2% of patients had incomplete tendon healing, and with the control, 30.5% of patients had incomplete tendon healing. There was a statistically significant difference in favor of PRP (RR, 0.57 [95% CI, 0.45-0.73]; $I^2 = 32\%$; $P < .05$).

Tendon Healing Rate in Small-Medium Tears. Tendon healing in small-medium tears was reported in 3 studies, with 76 patients treated with PRP and 81 with a control.

TABLE 3
Subgroup Analysis of LP-PRP and LR-PRP[a]

Outcome	No. of Patients, PRP/C	Outcome, PRP/C	Statistics	Favors
LP-PRP				
Tendon healing rate	283/278	17.0%/30.9%	RR, 0.55 (95% CI, 0.42 to 0.73); I^2 = 4%; $P < .05$	LP-PRP
Tendon healing rate in medium-large tears	105/98	6.7%/26.5%	RR, 0.25 (95% CI, 0.12 to 0.53); I^2 = 0%; $P < .05$	LP-PRP
VAS score at day 30	64/62	3.3/4.9	MD, –1.48 (95% CI, –1.77 to –1.14); I^2 = 8%; $P < .05$	LP-PRP
VAS score at final follow-up	113/111	0.6/0.9	MD, –0.22 (95% CI, –0.37 to –0.06); I^2 = 0%; $P < .05$	LP-PRP
Constant score	225/230	87.1/84.3	MD, 2.65 (95% CI, 0.90 to 4.41); I^2 = 0%; $P < .05$	LP-PRP
University of California, Los Angeles score	172/169	30.8/29.7	MD, 1.39 (95% CI, 0.61 to 2.17); I^2 = 0%; $P < .05$	LP-PRP
American Shoulder and Elbow Surgeons score	198/203	88.6/87.0	MD, 1.22 (95% CI, –0.65 to 3.09); I^2 = 0%; P = .20	None
LR-PRP				
Tendon healing rate	72/73	30.5%/40.7%	RR, 0.67 (95% CI, 0.37 to 1.11); I^2 = 0%; P = .36	None
Constant score	72/73	86.0/76.6	MD, 2.17 (95% CI, –0.48 to –4.82); I^2 = 0%; P = .11	None

[a]C, control; LP, leukocyte-poor; LR, leukocyte-rich; MD, mean difference; PRP, platelet-rich plasma; RR, risk ratio; VAS, visual analog scale.

With PRP, 22.4% of patients had incomplete tendon healing, and with the control, 38.3% of patients had incomplete tendon healing. There was a statistically significant difference in favor of PRP (RR, 0.59 [95% CI, 0.36-0.95]; I^2 = 0%; $P < .05$).

Tendon Healing Rate in Medium-Large Tears. Tendon healing in medium-large tears was reported in 4 studies, with 114 patients treated with PRP and 105 with a control. With PRP, 12.3% of patients had incomplete tendon healing, and with the control, 30.5% of patients had incomplete tendon healing. There was a statistically significant difference in favor of PRP (RR, 0.38 [95% CI, 0.23-0.64]; I^2 = 80%; $P < .05$). Because of significant heterogeneity, subgroup analysis was performed to evaluate tendon healing in medium-large tears when using leukocyte-poor PRP alone; there were 3 studies with 103 patients treated with PRP and 100 with a control. With PRP, 6.7% of patients had incomplete tendon healing, and with the control, 26.5% of patients had incomplete tendon healing. There was a statistically significant difference in favor of PRP (RR, 0.25 [95% CI, 0.12-0.53]; I^2 = 0%; $P < .05$).

Patient Satisfaction. Patient satisfaction was reported in 3 studies, with 93 patients treated with PRP and 94 with a control. With PRP, 86.0% of patients were satisfied, and with the control, 76.6% of patients were satisfied. There was no statistically significant difference (RR, 1.12 [95% CI, 0.98-1.29]; I^2 = 0%; P = .10).

VAS Score at Day 30. The VAS score at day 30 was reported in 3 studies, with 84 patients treated with PRP and 82 with a control. With PRP, the mean VAS score was 2.9, and with the control, the mean VAS score was 4.3. There was a statistically significant difference in favor of PRP (MD, –1.41 [95% CI, –1.69 to –1.13]; I^2 = 38%; $P < .05$).

VAS Score at Final Follow-up. The VAS score at final follow-up was reported in 4 studies, with 143 patients treated with PRP and 141 with a control. With PRP, the mean VAS score was 1.2, and with the control, the mean VAS score was 1.4. There was a statistically significant difference in favor of PRP (MD, –0.12 [95% CI, –0.20 to –0.05]; I^2 = 0%; $P < .05$).

Constant Score. The Constant score was reported in 9 studies, with 297 patients treated with PRP and 303 with a control. With PRP, the mean Constant score was 85.6, and with the control, the mean Constant score was 83.1. There was a statistically significant difference in favor of PRP (MD, 2.51 [95% CI, 1.04-3.97]; I^2 = 0%; $P < .05$).

UCLA Score. The UCLA score was reported in 6 studies, with 194 patients treated with PRP and 192 with a control. With PRP, the mean UCLA score was 30.9, and with the control, the mean UCLA score was 29.9. There was a statistically significant difference in favor of PRP (MD, 1.30 [95% CI, 0.55-2.05]; I^2 = 0%; $P < .05$).

ASES Score. The ASES score was reported in 5 studies, with 198 patients treated with PRP and 203 with a control. With PRP, the mean ASES score was 88.6, and with the control, the mean ASES score was 87.0. There was no statistically significant difference (MD, 1.21 [95% CI, –0.65 to 3.09]; I^2 = 0%; P = .20).

The results of subgroup analysis for leukocyte-poor and leukocyte-rich PRP can be found in Table 3.

Clinical Outcomes in PRF

Tendon Healing Rate. Tendon healing was reported in 6 studies, with 178 patients treated with PRF and 175 with a control. With PRF, 23.0% of patients had incomplete tendon healing, and with the control, 24.6% of patients had incomplete tendon healing. There was no statistically significant difference (RR, 0.95 [95% CI, 0.69-1.31]; I^2 = 10%; P = .74).

Patient Satisfaction. Patient satisfaction was reported in 2 studies, with 31 patients treated with PRF and 32 with a control. With PRF, 96.8% of patients were satisfied,

and with the control, 90.6% of patients were satisfied. There was no statistically significant difference (RR, 1.97 [95% CI, 0.93-1.23]; $I^2 = 0\%$; $P = .37$).

Constant Score. The Constant score was reported in 3 studies, with 96 patients treated with PRF and 96 with a control. With PRF, the mean Constant score was 80.8, and with the control, the mean Constant score was 79.8. There was no statistically significant difference (MD, 0.92 [95% CI, –0.71 to 2.54]; $I^2 = 70\%$; $P = .27$).

ASES Score. The ASES score was reported in 2 studies, with 48 patients treated with PRF and 52 with a control. With PRF, the mean ASES score was 88.5, and with the control, the mean ASES score was 89.7. There was no statistically significant difference (MD, –2.86 [95% CI, –6.51 to 0.79]; $I^2 = 46\%$; $P = .12$).

Operation Time. The operation time was reported in 2 studies, with 46 patients treated with PRF and 48 with a control. With PRF, the mean operation time was 99.1 minutes, and with the control, the mean operation time was 83.3 minutes. There was a statistically significant difference in favor of the control (MD, 11.98 [95% CI, 3.79-20.18]; $I^2 = 37\%$; $P < .05$).

DISCUSSION

The most important finding from this study was that PRP has clinical benefits in improving tendon healing rates in tears of all sizes, pain levels, and functional outcomes in rotator cuff repair. In contrast, our study demonstrated that PRF has no beneficial effect on tendon healing or clinical outcomes, with 1 study suggesting that it may have a negative effect on healing.[37] While several previous systematic reviews and meta-analyses have been performed, this was the first study to find that PRP was associated with a significant improvement in tendon healing rates in tears >3 cm. The most recent literature search was performed by Cai et al[6] in January 2015, and in the interim, 9 new studies have been published.[¶] This increase in included studies allowed for sufficient numbers to be subgrouped into PRP and PRF, as no other meta-analysis had done this. This increase in numbers also allowed for sufficient power to detect a difference in larger tears, as previous studies had found a significant difference in tears <3 cm[6,40,49] but for tears >3 cm, because they were limited by the lack of numbers to detect a difference. Previous studies have not identified a difference in functional outcomes when using PRP.

Our meta-analysis found that pain levels were significantly lower in the immediate postoperative period, a month after surgery, and at final follow-up when PRP was used compared with a control.[12,22,35] In the month after surgery, this effect was not just statistically significant but clinically significant as it reached the minimal clinically important difference of 1.4 on the VAS score.[29] While the functional outcomes assessed reached statistical significance in terms of the Constant score and UCLA score, these did not reach clinical significance. The difference in functional outcomes may be explained by the difference in tendon healing rates, as patients with incomplete tendon healing have been shown to have worse clinical outcomes than those with complete healing.[46]

Heterogeneity, the statistical measure of homogeneity, was low across all parameters measured, which suggests consistent effects throughout the studies.[14] The only outcome with high heterogeneity was tendon healing in tears >3 cm; however, when only studies with leukocyte-poor PRP were included, there was low heterogeneity and still statistical significance in favor of PRP over the control. It was not possible to assess this outcome in leukocyte-rich PRP alone. A study comparing the effect of leukocyte-rich PRP and leukocyte-poor PRP in arthroscopic rotator cuff repair would be very beneficial to our understanding of PRP's clinical effects on tendon healing and the effect of leukocyte concentration. Basic science supports the use of both leukocyte-poor and leukocyte-rich PRP in tendon healing, but leukocyte-poor PRP has been shown to promote normal collagen synthesis and decrease inflammatory cytokines to a greater extent.[10] Our study found leukocyte-poor PRP to be equivalent or better than leukocyte-rich PRP, but the number of included patients treated with leukocyte-rich PRP was smaller and may cause it to be underpowered.

Basic science studies have shown the potential benefit of PRP for tendon healing, which has led to these recent RCTs.[2] In vitro studies have shown that the growth factors in PRP, including TGF, PDGF, insulin-like growth factor 1, hepatocyte growth factor, vascular endothelial growth factor, and fibroblast growth factor, can influence healing and reduce inflammation.[45] In vivo studies have also shown that PRTs improve vascularity, tendon repair time, fiber organization, and tensile strength.[2,4] Cole et al[10] analyzed the enzyme-linked immunosorbent assay (ELISA) results of the proinflammatory and anti-inflammatory markers in PRP injections in osteoarthritic knees and found that PRP resulted in lower concentrations of the inflammatory markers IL-1β and TNF-α in vivo. No study has analyzed the ELISA results of PRP in the rotator cuff, but basic science studies have shown that PRP inhibits the catabolic effects of IL-1, IL-1RA, IL-6, IL-8, and MMP-9 on tendon cells.[11]

There are limitations in recommending routine PRP in arthroscopic rotator cuff repair, as there is still uncertainty in the composition of PRP. With an assortment of PRP preparations, there are differences in the platelet count, leukocyte count, and growth factor concentration that vary depending on the patient characteristics and preparation kits used. Rodeo et al[37] proposed that a sample of the delivered PRP be measured for these factors and cytokines to evaluate this. Furthermore, comparison of patients' baseline blood characteristics and their correlation to postoperative outcomes warrants further research, as it may allow us to select patients who may benefit more from PRP. The optimal dosage and timing intervals of injections also remain areas of concern, as they may affect the postoperative course and there is no literature to support any injection protocol.

While it has been proposed that PRF would be more beneficial than PRP because of the prolonged release of cytokines over days and not hours, it was shown that

[¶]References 12, 15, 19, 22, 28, 37, 43, 50, 54.

PRF had no benefit in any single study in terms of tendon healing, tendon vascularity, or functional outcomes.[37] There was also low heterogeneity across all outcomes measured, suggesting that these effects were consistent. Rodeo et al[37] found that PRF may do the opposite and inhibit tendon healing. They proposed that as the clot is made of fibrin, it has to be sutured in and may have a space-occupying effect between the tendon and bone, which results in a gap after it dissolves.[37] Additionally, Hasan et al[20] found that in a rat model, PRF results in exuberant and disorganized healing, characterized by fibrovascular scar tissue. Zumstein et al[52,54] found that PRF has a quarter of the growth factors that PRP does, which may be insufficient to improve tendon healing and lead to inferior results. The preparation and application of PRF also resulted in a significantly increased operation time, which results in increased costs and decreased operating theater efficiency.[44,54] Therefore, on the basis of these findings, there is no evidence that PRF should be used in arthroscopic rotator cuff repair.

Limitations

As this is a systematic review, the limitations in all included studies are present in this study. There is a multitude of confounding factors that may affect the results, including the lack of standardization in the operative technique, as some studies used double-row repair and others used single-row repair. There was also an inability to completely stratify tear sizes, as most studies used a combination of all tear sizes. Because of the underreporting of these variables across the studies, it was not possible to completely account for all of the factors affecting outcomes. While we were able to stratify our results into PRP and PRF, and subsequently analyze some of the outcome measures based on leukocyte concentration, it would be of benefit to subgroup these further based on the number of platelets, growth factors, and other bioactive cytokines. However, only 6 of 18 reported approximations of the number of platelets in the prepared PRP/PRF, and only 1 of these studies used cellular analysis of their own patients. Despite these limitations in the reported data, the heterogeneity was low across the outcome measures, indicating that there were consistent outcomes across the studies. On further subgroup analysis of leukocyte-poor and leukocyte-rich PRP, heterogeneity was almost nonexistent. However, the problem with the subgroup analysis was that the outcome measures might be insufficiently powered in the leukocyte-rich PRP group, as there were only 145 patients analyzed.

CONCLUSION

The current evidence shows that using PRP in rotator cuff repair results in improved healing rates, pain levels, and functional outcomes. In contrast, PRF has been shown to have no benefit in improving tendon healing rates or functional outcomes.

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