The Effect of Platelet-Rich Plasma Leukocyte Concentration on Arthroscopic Rotator Cuff Repair

CME

A Network Meta-analysis of Randomized Controlled Trials

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Background: It is unclear whether leukocyte-poor (LP) or leukocyte-rich (LR) varieties of platelet-rich plasma (PRP) as an adjuvant to arthroscopic rotator cuff repair (ARCR) result in improved tendon healing rates.

Purpose: To perform a network meta-analysis of the randomized controlled trials in the literature to ascertain whether there is evidence to support the use of LP- or LR-PRP as an adjunct to ARCR.

Methods: The literature search was based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Randomized controlled trials comparing LP- or LR-PRP with a control alongside ARCR were included. Clinical outcomes, including retears and functional outcomes, were compared using a frequentist approach to network meta-analysis, with statistical analysis performed using R. The treatment options were ranked using the P-score.

Results: There were 13 studies (868 patients) included, with 9 studies comparing LP-PRP with a control and 4 studies comparing LR-PRP with a control. LP-PRP was found to significantly reduce the rate of retear and/or incomplete tendon healing after fixation, even among medium-large tears; it also improved outcomes on the visual analog scale for pain, Constant score, and University of California Los Angeles score. LP-PRP had the highest P-score for all treatment groups. LR-PRP did not result in any significant improvements over the control group, except for visual analog scale score for pain. However, post hoc analysis revealed that LP-PRP did not lead to significant improvements over LR-PRP in any category.

Conclusion: The current study demonstrates that LP-PRP reduces the rate of retear and/or incomplete tendon healing after ARCR and improves patient-reported outcomes as compared with a control. However, it is still unclear whether LP-PRP improves the tendon healing rate when compared with LR-PRP.

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

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Rotator cuff tears are a common clinical pathology, with >250,000 to 300,000 arthroscopic repairs performed in the United States annually.[4] Despite every effort of the surgeon to optimize the bone-tendon interface at the time of repair, rates of incomplete tendon healing range between 20% and 95%, which has been shown to result in worse clinical outcomes.[27,39] As a response, adjuvant platelet-rich plasma (PRP) therapies have become increasingly popular in an effort to augment tendon healing after arthroscopic rotator cuff repair (ARCR).[15]

PRP is an autologous blood product containing a high concentration of platelets, growth factors, and cytokines, which basic science studies have shown may improve tendon healing.[1] Dohan Ehrenfest et al[7] classified PRP preparations into 4 subtypes: leukocyte-poor (LP) pure PRP, leukocyte-rich (LR) pure PRP, LP platelet-rich fibrin matrix (PRFM), and LR-PRFM. Hurley et al[15] demonstrated in their

systematic review that the use of LP or LR pure PRP as an adjuvant to ARCR resulted in significantly improved functional outcomes and substantially reduced the rates of incomplete tendon healing in rotator cuff tears of all sizes. However, the authors could not determine whether LP- or LR-PRP was more beneficial, and they found that PRFM did not improve tendon healing rates.

While there is evidence to support the use of PRP as an adjunct to ARCR, there is no general consensus on the optimal PRP preparation with respect to leukocyte concentration.[16,30] The purpose of the current study is to perform a network meta-analysis of the randomized controlled trials (RCTs) in the literature to ascertain whether there is evidence to support the use of LP- or LR-PRP as an adjunct to ARCR. Our hypothesis was that there would be no superior method of PRP preparation as an adjunct to ARCR and that both methods would show efficacy in improving tendon healing rates.

METHODS

Study Selection

Two independent reviewers (E.T.H., C.A.C.) performed the literature search based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[41] Any discrepancies were reviewed and arbitrated by a third author (E.J.S.). 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 Database in March 2020 with the search algorithm: (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 platelet OR platelet-rich). No time limit was given to publication date.

Eligibility Criteria

RCTs comparing PRP with a control in ARCR that were published in peer-reviewed journals were included. Nonrandomized and nonclinical studies were excluded. Additionally, studies evaluating PRFM were excluded, as this preparation type has strong evidence establishing that it is not effective as an adjunct to ARCR.[15]

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 the same 2 independent reviewers using a predetermined data sheet. Studies were defined as LP-PRP or LR-PRP by the manufacturer's specifications and whether they had more or fewer leukocytes than autologous blood. The level of evidence was based on the criteria set by the Oxford Centre for Evidence-Based Medicine. The risk of bias and methodological quality of evidence (MQOE) were assessed for RCTs using the 5-point Jadad scale.[17] Studies with a Jadad score >3 were considered to have a low risk of bias.

Statistical Analysis

All statistical analyses were performed using R (R Foundation for Statistical Computing). A frequentist approach to network meta-analysis with a random effects model was performed using the *netmeta* package Version 0.9-6 in R.[28] For continuous outcomes, the relative effect sizes were reported as standardized mean differences (MDs), and for dichotomous outcomes, the relative effect sizes were reported as odds ratios (ORs). The effect sizes were reported with 95% CIs and compared with the control group as the standard comparator. Heterogeneity was quantified using the I^2 statistic.[12] The frequentist analog to the surface under the cumulative ranking probabilities called the P-score was used to rank the treatments. The P-score represents the probability that the treatment option is the ideal method for an optimal result in each outcome measure.[28]

RESULTS

The initial literature search identified 841 studies. Once duplicates were removed and the articles were screened for inclusion and exclusion criteria, the full text of 532 studies was assessed for eligibility. Thirteen RCTs with 868 patients were included in this review (Figure 1). Seven studies were excluded because 6 used PRFM and 1 evaluated acromioplasty without ARCR.[3,10,26,35,42,43]

Study Characteristics

In total, 13 RCTs compared 433 patients treated with PRP and 435 treated with a control.[‡] Nine studies used LP-PRP and 4 used LR-PRP. Eleven RCTs used PRP at the end of the procedure, and 2 used it postoperatively. All included studies were level 1 RCTs, with a mean MQOE score of 3.9 ± 0.6 (mean ± SD). Only 1 had a low score and was considered a high risk of bias.[40] Six studies performed hematological analysis, including platelet concentration analysis. All studies used PRP at the bone-tendon interface; 1 study also used it in the subacromial space; and 1 also used it intratendinously. The most common modality to evaluate tendon healing was magnetic resonance imaging alone (9 studies), with 2 studies using ultrasound and 1 using magnetic resonance imaging and computed tomography angiography. The study characteristics are reported in Table 1.

[‡]References 6, 8, 9, 11, 13, 19-21, 23, 24, 29, 33, 34, 40.

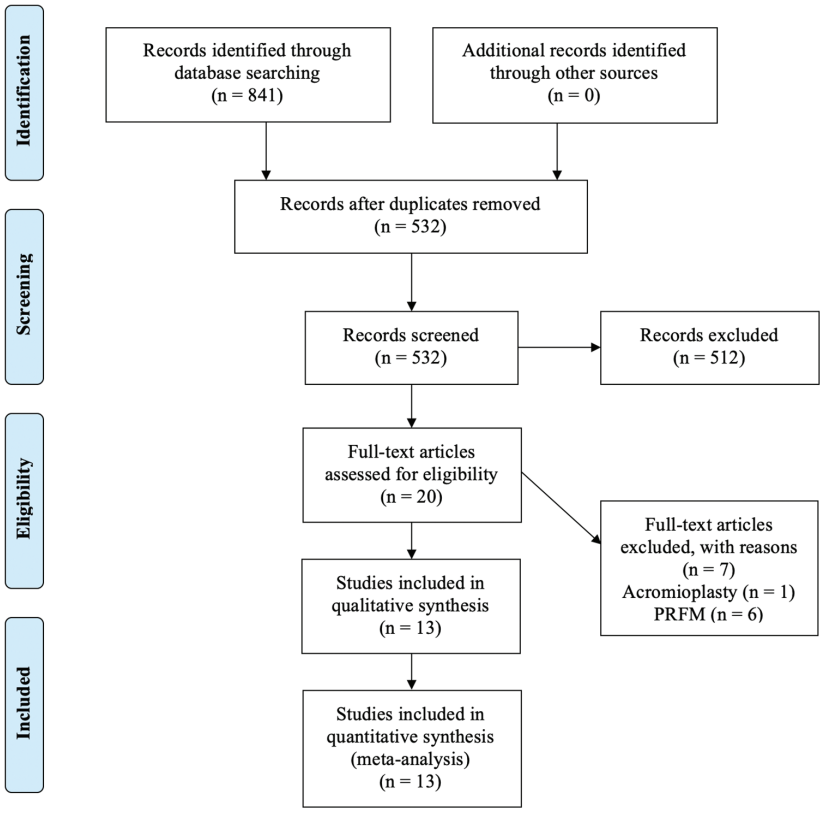

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study selection flow diagram. PRFM, platelet-rich fibrin matrix.

Tendon Healing Rate

The retear and/or incomplete tendon healing rate was reported in 12 studies.[§] Overall, LP-PRP had the highest P-score (0.8642) and resulted in a significantly lower retear and/or incomplete tendon healing rate than the control (OR, 0.42; 95% CI, 0.26-0.69). LR-PRP did not result in a lower retear and/or incomplete tendon healing rate as compared with the control group (OR, 0.55; 95% CI, 0.27-1.11). Post hoc analysis revealed no difference in LP-PRP versus LR-PRP (OR, 0.77; 95% CI, 0.33-1.80). There was low heterogeneity in the outcomes between the groups ($I^2 = 0$). The forest plot of the control group versus LP-PRP and LR-PRP for incomplete tendon healing is shown in Figure 2.

Tendon Healing Rate in Medium-Large Tears

The retear and/or incomplete tendon healing rate in medium-large tears was reported in 4 studies. Overall, LP-PRP had the highest P-score (0.9004) and resulted in a significantly lower incomplete tendon healing rate than the control (OR, 0.17; 95% CI, 0.07-0.45). LR-PRP did not result in a lower incomplete tendon healing rate as compared with the control group (OR, 0.58; 95% CI, 0.04-8.15). Post hoc analysis revealed no difference in LP-PRP versus LR-PRP (OR, 0.29; 95% CI, 0.02-4.93). There was low heterogeneity in the outcomes between the groups ($I^2 = 0$). The forest plot of the control group versus LP-PRP and LR-PRP for incomplete tendon healing in medium-large tears is shown in Figure 3.

Visual Analog Scale

The visual analog scale (VAS) for pain was reported in 5 studies.[19-21,23,40] Overall, LP-PRP had the highest P-score (0.9999) and resulted in a significantly lower VAS score than the control (MD, –0.21; 95% CI, –0.36 to –0.06). LR-PRP also resulted in a lower VAS score as compared with the control group (MD, –0.10; 95% CI, –0.18 to 0.02). Post hoc analysis revealed no difference in LP-PRP versus LR-PRP (MD, –0.11; 95% CI, –0.28 to 0.06). There was low heterogeneity in the outcomes between the groups ($I^2 = 0$). The forest plot of the control group versus LP-PRP and LR-PRP for VAS score is shown in Figure 4.

Constant Score

The Constant score was reported in 10 studies.[‖] Overall, LP-PRP had the highest P-score (0.7588) and resulted in a significantly higher Constant score than the control (MD, 2.26; 95% CI, 0.55-3.97). LR-PRP did not result in

[§]References 6, 8, 9, 13, 19, 20, 21, 23, 24, 29, 33, 34, 40.

[‖]References 6, 8, 9, 13, 19, 20, 21, 23, 24, 33, 40.

TABLE 1
Study Characteristics[a]

First Author (Year)[b]	MQOE	LP/LR	PRP/C, No.	Age, y[c]	Preparation Kit	Injection Volume, mL	Platelet Concentration × 10^3	Activating Agent	Applied Site	Visualization	Follow-up, mo
D'Ambrosi (2016)[6]	5	LR	20/20	60 ± 9.4	GPS (Biomet Biologics)	16			BTI	No	6
Flury (2016)[9]	4	LP	60/60	58.4 ± 8.1	ACP (Arthrex)	4			BTI	No	24
Hak (2015)[11]	4	LP	12/13	55.0 ± 6.4	ACP (Arthrex)	6-9			BTI + SAS	Direct	1.5
Holtby (2016)[13]	4	LP	41/41	59.0 ± 8.0	SmartPReP 2 (Harvest Technologies Corp)	7			BTI	Direct	6
Jo (2013)[19]	4	LP	24/24	63.1 ± 7.3	COBE Spectra (Terumo BCT)	9	1000	Calcium gluconate	BTI	No	12
Jo (2015)[20]	4	LP	37/37	61.1 ± 6.1	COBE Spectra (Terumo BCT)	9	1000	Calcium gluconate	BTI	No	12
Malavolta (2018)[21]	4	LP	22/22	55.0 ± 7.5	Haemonetics MCS1 (Haemonetics Corp)	10		Calcium chloride	BTI	No	60
Pandey (2016)[23]	4	LP	56/54	54.5 ± 8.4	Heraeus Cryofuge (Thermo Cyrofuge)	8	474	Calcium chloride	BTI	No	12
Randelli (2011)[24]	4	LR	26/27	60.6 ± 9.5	GPS (Biomet Biologics)	6		Calcium chloride	BTI	No	24
Ruiz-Moneo (2013)[29]	4	LP	32/31	55.5 ± 9.9	PRGF System 1 (BTI)	1	600	Calcium chloride	BTI + IT	Direct	12
Snow (2020)[33]	4	LR	40/47		GPS (Biomet Biologics)	6		Clotalyst Autologous Activation System (Biomet)	BTI	Ultrasound	12
Wang (2015),[34] Ebert (2017)[8]	4	LP	30/30	59.1 ± 10.9	ACP (Arthrex)	2 × 2-4	470	Calcium chloride	BTI	Ultrasound	4
Zhang (2016)[40]	2	LR	32/30	57.1 ± 6.7	GPS (Biomet Biologics)			Calcium chloride	BTI	Direct	12

[a]Blank cells indicate *not reported*. BTI, bone-tendon interface; C, control; IT, intratendon; LP, leukocyte poor; LR, leukocyte rich; MQOE, methodological quality of evidence; PRP, platelet-rich plasma; SAS, subacromial space.
[b]For each study: level of evidence, 1.
[c]Mean ± SD.

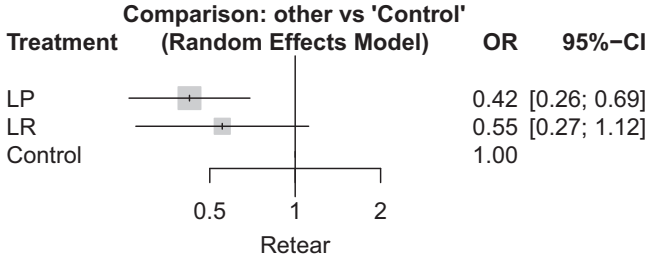

Figure 2. Forest plot of incomplete tendon healing. LP, leukocyte poor; LR, leukocyte rich; OR, odds ratio.

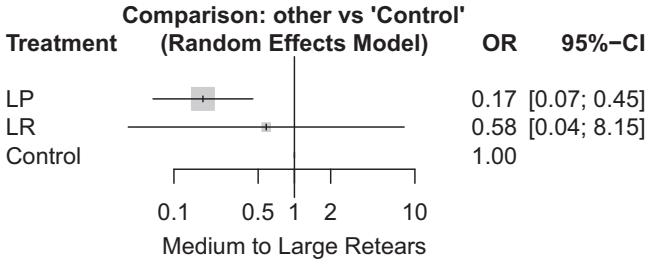

Figure 3. Forest plot of incomplete tendon healing in medium-large tears. LP, leukocyte poor; LR, leukocyte rich; OR, odds ratio.

a higher Constant score as compared with the control group (MD, 2.17; 95% CI, –0.48 to 4.82). Post hoc analysis revealed no difference in LP-PRP versus LR-PRP (MD, 0.09; 95% CI, –3.06 to 3.24). There was low heterogeneity in the outcomes between the groups (I^2 = 0). The forest plot of the control group versus LP-PRP and LR-PRP for Constant score is shown in Figure 5.

UCLA Score

The University of California Los Angeles (UCLA) score was reported in 6 studies.[19-21,23,24,29] Overall, LP-PRP had the highest P-score (0.8726) and resulted in a significantly

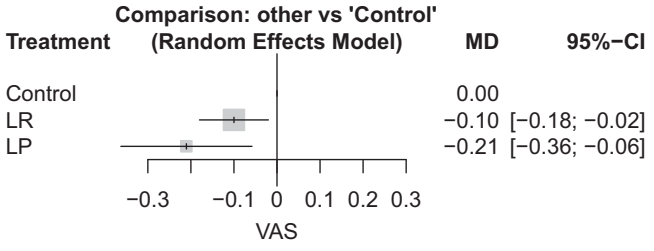

Figure 4. Forest plot of VAS score. LP, leukocyte poor; LR, leukocyte rich; MD, mean difference; VAS, visual analog scale.

TABLE 2
P-Scores[a]

	Incomplete Tendon Healing	Incomplete Tendon Healing in Medium-Large Tears	VAS Score	Constant Score	UCLA Score
LP	0.8642	0.9004	0.9999	0.7589	0.8726
LR	0.6111	0.4273	0.4504	0.7118	0.4051
Control	0.0247	0.1722	0.0496	0.0293	0.2223

[a]LP, leukocyte poor; LR, leukocyte rich; UCLA, University of California Los Angeles; VAS; visual analog scale.

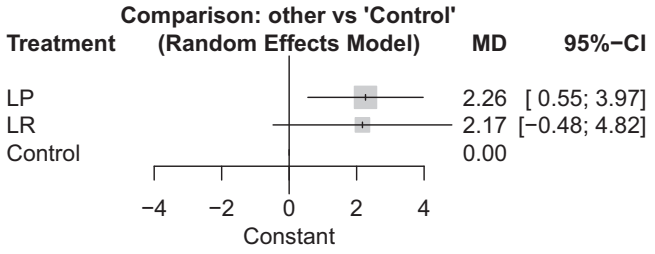

Figure 5. Forest plot of Constant score. LP, leukocyte poor; LR, leukocyte rich; MD, mean difference.

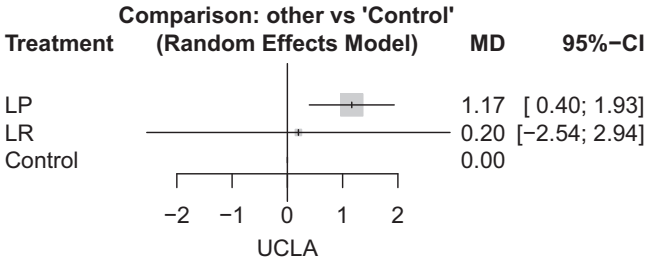

Figure 6. Forest plot of UCLA score. LP, leukocyte poor; LR, leukocyte rich; MD, mean difference; UCLA, University of California Los Angeles.

higher UCLA score than the control (MD, 1.17; 95% CI, 0.40 to 1.93). LR-PRP did not result in a higher UCLA score as compared with the control group (MD, 0.20; 95% CI, –2.54 to 2.94). Post hoc analysis revealed no difference in LP-PRP versus LR-PRP (MD, 0.96; 95% CI, –1.88 to 3.81). There was low heterogeneity in the outcomes between the groups ($I^2 = 0$). The forest plot of the control group versus LP-PRP and LR-PRP for UCLA score is shown in Figure 6.

The P-scores are shown in Table 2, and all individual study outcomes are shown in Table 3.

DISCUSSION

The most important finding in this study was that LP-PRP was shown to significantly reduce the rate of incomplete tendon healing and/or retear as compared with a control group. Additionally, the use of LP-PRP led to an overall significant reduction in pain and improvement in patient-reported outcomes. LR-PRP demonstrated similar improvements in pain when compared with a control group. However, owing to inadequate power, there was a less clear difference in the other measures when comparing LR-PRP with a control group. It was not possible to determine whether the results differed between LP-PRP and LR-PRP; as no studies were identified on this topic, further trials are warranted.

A network meta-analysis allows for direct and indirect comparison of treatments using common comparators and for them to be ranked using the P-score. The P-score represents the probability that the treatment option is the ideal method for an optimal result in each outcome measure.[28] The P-score does not represent the magnitude of difference between the treatment choices, and it does not signify clinically significant differences. Thus, it is important to examine the OR, MD, and 95% CI between each treatment group, as this allows for a true comparison of the relative outcomes between the procedures. The OR shows the odds of an event's occurring versus the control, and the MD shows the difference in the outcome score as compared with the control.

PRP contains platelets, growth factors, and cytokines, such as vascular endothelial growth factor, insulin-like growth factor, fibroblast growth factor, platelet-derived growth factor, transforming growth factor ß, and epidermal growth factor.[1,2,22] Basic science studies have shown that PRP can improve tendon healing by promoting angiogenesis, cellular migration, cellular proliferation, and matrix deposition, which lead to increased tenocyte proliferation.[1] In a systematic review of the basic science literature, Baksh et al[1] found that PRP improved tendon repair time, tendon tensile strength, and tendon vascularity. Additionally, PRP contains pro- and anti-inflammatory factors that depend on the leukocyte concentration; these interactions promote M2 macrophage upregulation, modulate cytokine production, and facilitate tissue repair.[36]

The effect of leukocyte concentration on PRP has been shown to be paramount in its efficacy, with different concentrations being favored for different pathologies.[14,25,32,38] Thus, there has been increasing interest in identifying the optimal PRP subgroup for each indication. In a rotator cuff tendon model, Cross et al[5] determined that LP-PRP promotes normal collagen matrix synthesis and decreases cytokines associated with matrix degradation and inflammation to a greater extent than LR-PRP. However, the authors showed

TABLE 3
Clinical Outcomes in Individual Studies[a]

	Retear	Retear in Medium-Large Tears	VAS	Constant Score	UCLA Score
Leukocyte-poor PRP					
Flury (2016)[9]	10.2 vs 16.7			82.7 (8) vs 82.1 (9.5)	
Hak (2015)[11]			3.6 (2.2) vs 3.9 (3.3)		
Holtby (2016)[13]	36.1 vs 52.6			108 (19) vs 103 (24)	
Jo (2013)[19]	20 vs 55.5	20 vs 55.5	0.8 (1) vs 1.2 (1.8)	79.1 (13.4) vs 82 (13)	30.1 (4) vs 29.2 (6)
Jo (2015)[20]	3.3 vs 20	3.3 vs 20	1.1 (1.3) vs 1.5 (1.7)	74.7 (9.2) vs 70.9 (9.8)	30.7 (4.2) vs 29.5 (4.7)
Malavolta (2018)[21]	31.8 vs 50		1.5 (2.1) vs 1.4 (1.8)	82 (9.5) vs 82.1 (11)	32.5 (3.8) vs 32.1 (4.6)
Pandey (2016)[23]	4 vs 19.2	4 vs 19.2	0.1 (0.3) vs 0.3 (0.5)	92.6 (5.1) vs 88.9 (8.5)	34.7 (0.7) vs 33.1 (3.7)
Ruiz-Moneo (2013)[29]	65.6 vs 70.6				23.2 (4.9) vs 23.8 (5.7)
Wang (2015),[34] Ebert (2017)[8]	0 vs 6.7		3.1 (0.1) vs 3.2 (0.2)	86.2 (11.4) vs 85.2 (11.3)	
Leukocyte-rich PRP					
D'Ambrosi (2016)[6]	0 vs 0			81 (11.2) vs 78.5 (9)	
Randelli (2011)[24]	40.9 vs 52.2	77.8 vs 85.7		82.4 (6.3) vs 78.7 (10)	31.2 (5.2) vs 31 (4.1)
Snow (2020)[33]	15.4 vs 21.1				
Zhang (2016)[40]	13.3 vs 30				

[a]Blank cells indicate *not reported*. Values are presented as PRP group vs control group and in percentages or mean (SD). PRP, platelet-rich plasma; UCLA, University California, Los Angeles; VAS, visual analog scale.

that neither LP-PRP nor LR-PRP enhanced matrix synthesis in severely degenerative tendons. In a tendinopathy model, Yan et al[38] demonstrated that LP-PRP had greater anabolic effects than LR-PRP, yet both were better than a saline placebo control. In contrast, Jiang et al[18] found higher gene expression and more protein synthesis of collagen I with LR-PRP than with LP-PRP, which led to more mature collagen fibers, larger fiber diameter, higher failure load, and higher tensile stress. In summary, evidence in support of an optimal leukocyte concentration of PRP remains contested.

In our network meta-analysis, we established that there is a definitively lower incomplete tendon healing rate with LP-PRP than with control. However, it was unclear whether LR-PRP reduced the rate of incomplete tendon healing, which may be due to insufficient power yielded by the 4 included studies on LR-PRP. Furthermore, it was not possible to detect a statistically significant difference between LP-PRP and LR-PRP, as they had similar effects when compared with the common comparator controls. In a recent systematic review, Yang et al[39] found significantly worse outcomes in patients with incomplete tendon healing than those with successful repairs. This closely correlates with our findings that, given the reduction in incomplete tendon healing, there was an overall significant benefit with LP-PRP in patient-reported outcomes. Samuelson et al[31] demonstrated that adjuvant PRP in ARCR would not be cost-effective unless retear rates were reduced by at least 9.1%. However, our analysis of LP-PRP alone demonstrates that it may be cost-effective because of its ability to significantly reduce incomplete healing rates. While basic science supports that LP-PRP and LR-PRP both improve tendon tissue quality and tensile strength, it is unclear whether this contributes to any improvement in functional outcomes in those with successful repairs.

Although there is evidence to support the use of LP-PRP alongside ARCR, there are still questions that require further study. As it is still unclear whether LP-PRP or LR-PRP is superior, an RCT comparing the 2 preparations would be of interest. Such a study would require large patient numbers to achieve sufficient power—as most of the existing studies in the literature have been too small to detect a difference. Aside from leukocyte concentration, there are other constituent factors in PRP that may affect the clinical outcome, including platelet count, growth factor concentration, and whether the PRP is activated. All of these variables may be influenced by patient characteristics and preparation method, although it is unclear how these affect postoperative outcomes.[2,22,37] This should be another topic of future investigation.

Limitations

There are limitations in the validity of network meta-analysis, as the findings are dependent on the quality of the studies included and the actual number of studies comparing each outcome. Unfortunately, not all included studies compared all patient-reported outcomes, which limits the power of the comparisons. Additionally, there were no studies comparing LP-PRP and LR-PRP, so all comparisons are indirect and based on common comparators. However, this is a strength of the network meta-analysis model and does allow comparison of these 2 groups. Bias was mitigated by the inclusion of only RCTs, and the heterogeneity was 0% across all measures.

CONCLUSION

The current study demonstrates that LP-PRP reduces the rate of retear and/or incomplete tendon healing after ARCR and subsequently improves patient-reported

outcomes as compared with a control. However, it is still unclear whether LP-PRP improves the tendon healing rate when compared with LR-PRP.

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