Platelet-Rich Plasma

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KEYWORDS

• Platelet-rich plasma • PRP • Orthobiologics • Regenerative medicine
• Tendinopathy • Osteoarthritis • Augmentation

KEY POINTS

- There is abundant high-quality level I evidence to recommend leukocyte-rich platelet-rich plasma (LR-PRP) injections for lateral epicondylitis and LP-PRP injections for osteoarthritis of the knee.
- There is a moderate amount of high-quality level I evidence to recommend LR-PRP injections for patellar tendinopathy and PRP injections for plantar fasciitis.
- There is currently insufficient high-quality evidence for recommendation, but small clinical trials have shown promising efficacy for PRP injections for rotator cuff tendinopathy, osteoarthritis of the hip, donor site pain in anterior cruciate ligament (ACL) reconstruction with patellar tendon autograft, and LP-PRP injections for high ankle sprains.
- The best available clinical evidence does not demonstrate efficacy of PRP injections for Achilles tendinopathy, acute fracture, or nonunion; surgical augmentation with PRP in rotator cuff repair, Achilles tendon repair, and ACL reconstruction; and efficacy has not been shown with PRP injections for muscle injuries, although preclinical studies suggest platelet-poor plasma may hold promise for muscle injuries, but clinical trials will be necessary to validate this.

INTRODUCTION

Platelet-rich plasma (PRP) is an autologous concentration of human platelets in a small volume of plasma produced by centrifuging a patient's own blood. Platelets contain a milieu of growth factors and mediators in their alpha granules (transforming growth factor [TGF]-β1, platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, insulinlike growth factor [IGF]-1),[1,2] which are concentrated through the centrifugation process and then be delivered to an injury site to augment the body's natural healing process.[3] The normal human platelet count ranges anywhere from 150,000 to 350,000/μL. Improvements in

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bone and soft tissue healing properties have been demonstrated with concentrated platelets of 1,000,000/μL, and thus it is this concentration of platelets in a 5-mL volume of plasma that has been suggested as one working definition of PRP.[2,4] Another proposed definition of PRP is any plasma fraction that concentrates platelets greater than baseline. A resultant threefold to fivefold increase in growth and differentiation factors can be expected with PRP compared with normal nonconcentrated whole blood. PRP preparations are typically further categorized into leukocyte-rich PRP (LR-PRP) preparations, defined as having a neutrophil concentration above baseline, and leukocyte-poor PRP (LP-PRP) preparations, defined as having a leukocyte (neutrophil) concentration below baseline.

PREPARATION AND COMPOSITION

Currently more than 16 commercial PRP systems are available on the market, and hence quite a bit of variation exists in the PRP collection and preparation protocol depending on the commercial system being used (**Table 1**), which gives each system's PRP unique properties.[1,7–9] Each commercial system has a different platelet capture efficiency that results in different whole-blood volume requirements to achieve the necessary final platelet concentration for PRP. The commercial systems may also differ in their isolation method (1-step or 2-step centrifugation), the speed of centrifugation, and the type of collection tube system and operation. Generally, whole blood is usually collected and mixed with an anticoagulant factor, such as acid-citrate-dextrose, sodium citrate, or ethylene diamine tetra-acetic acid. Centrifugation then separates red blood cells (RBCs) from platelet-poor plasma (PPP) and the "buffy coat," which contains the concentrated platelets ± leukocytes. The platelet-concentrated layer is isolated using various processing techniques, and the RBC and PPP layers may be discarded. The platelets can then be directly injected into the patient or be "activated" via the addition of either calcium chloride or thrombin, which then causes the platelets to degranulate and release the growth and differentiation factors. Approximately 70% of the stored growth factors are released within the first 10 minutes of activation, and nearly 100% of the growth factors are released within 1 hour of activation.[2,4] Small amounts of growth factors may continue to be produced by the platelet during the remainder of its life span (8–10 days).

The specific composition of PRP, however, likely varies not only from person to person but also when the isolation process is repeated in the same individual.[9] Both patient-specific factors, including medications taken, and commercial system preparation methods are known to influence the specific makeup of PRP.[8–10] The variability in the cellular composition of PRP preparations creates challenges in interpretation of the literature regarding the clinical efficacy of PRP.

Our current understanding appears to suggest that PRP with elevated leukocyte content, that is, leukocyte (neutrophil)-rich PRP (LR-PRP), is associated with proinflammatory effects.[8] The elevated leukocyte (neutrophil) concentrations present in LR-PRP are also associated with elevated catabolic cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and metalloproteinases,[10,11] which may antagonize the anabolic cytokines contained within platelets. The clinical ramifications and cellular effects of these different PRP preparations, including leukocyte content, are still currently being elucidated. To better evaluate and summarize the best quality evidence available for various clinical indications for different PRP preparations, we have performed a systematic review of the literature, and present our methods and results in the following sections.

Table 1
Characteristics of PRP preparations from different commercially available systems

System	Company	Blood Volume Required, mL	Concentrated Volume Produced, mL	Processing Time, min	PPP Produced?	Increase in [Platelets], Times Baseline	Platelet Capture Efficiency, % Yield
Leukocyte-rich PRP							
Angel	Arthrex (Florida, USA)	52[5]	1–20[a]	17[5]	+	10[a]	56%–75%[5]
GenesisCS	EmCyte (Florida, USA)	54[5]	6[5]	10[5]	+	4–7[5]	61% ± 12%[5]
GPS III	Biomet (Now known as Zimmer Biomet, Indiana, USA)	54[5]	6[5]	15[5]	+	3–10[5]	70% ± 30%[5]
Magellan	Isto Biologics/ Arteriocyte (Now known as Isto Biologics, Massachusetts, USA)	52[5]	3.5-7[5]	17[5]	+	3–15[5]	86% ± 41%[5]
SmartPReP 2	Harvest (Now known as Terumo BCT, Colorado, USA)	54[5]	7[5]	14[5]	+	5–9[5]	94% ± 12%[5]
Leukocyte-poor PRP							
Autologous Conditioned Plasma (ACP)	Arthrex	11[6]	4[6]	5[6]	–	1.3[6]	48% ± 7%[6]
Cascade	MTF (New Jersey, USA)	18[7]	7.5[7]	6[7]	–	1.6[7]	68% ± 4%[7]
Clear PRP	Harvest	54[a]	6.5[a]	18[a]	+	3–6[a]	62% ± 5%[a]
Pure PRP	EmCyte	50[a]	6.5[a]	8.5[a]	+	4–7[a]	76% ± 4%[a]

Abbreviations: PPP, platelet-poor plasma; PRP, platelet-rich plasma.
Plus minus sign signifies reported variance of platelet capture efficiency.
[a] Data obtained from manufacturers' promotional literature or internal studies.

TREATMENT OF TENDON INJURIES

PRP has been most actively evaluated in the treatment of tendon injuries or tendinopathies (**Table 2**). Tendons and ligaments heal through a dynamic process, with stages of inflammation, cellular proliferation, and subsequent tissue remodeling. Many of the cytokines found in PRP are involved in the signaling pathways that occur during this restorative process.[1,2] PRP may also promote neovascularization, which may not only increase the blood supply and nutrients needed for cells to regenerate the injured tissue, but may also bring new cells and remove debris from damaged tissue. Both these mechanisms of action are particularly attractive in chronic tendinopathy conditions in which the biologic milieu may be unfavorable for tissue healing. A recent systematic review and meta-analysis by Miller and colleagues[42] concluded that injections of PRP were more efficacious than control injections for treatment of symptomatic tendinopathy.

Lateral Epicondylitis

Clinical studies have evaluated PRP in lateral epicondylitis for patients who have failed to respond to physical therapy. In the largest such study, Mishra and colleagues[20] evaluated 230 patients who failed to respond to at least 3 months of conservative treatment for lateral epicondylitis in a prospective cohort study. Patients were treated with LR-PRP and at 24 weeks, the patients who received LR-PRP reported a 71.5% improvement in their pain scores compared with a 56.1% improvement in the control group ($P = .019$). The percentage of patients reporting significant residual elbow tenderness at 24 weeks was 29.1% in the patient group receiving PRP compared with 54.0% in the control group ($P = .009$). There was a clinically meaningful and statistically significant improvement at 24 weeks in patients treated with LR-PRP versus active control injection of local anesthetic.

PRP may also provide longer continuous relief of symptoms for lateral epicondylitis than corticosteroid injection and therefore have a more sustainable treatment effect. Gosens and colleagues[17] and Peerbooms and colleagues[43] evaluated the efficacy of LR-PRP versus corticosteroids in 100 patients who had a minimum 6-month history of recalcitrant chronic epicondylitis and had failed to respond to conservative management. Treatment success within this study was defined as, at minimum, a 25% reduction in the visual analog scale (VAS) score or Disability of Arm, Shoulder, and Hand score without a repeat intervention after 1 year. Although both groups improved in VAS scores from baseline, 73% (37 of 51 patients) in the PRP group versus 49% (24 of 49 patients) in the corticosteroid group were considered to have a successful response at 1 year ($P<.001$). Furthermore, 73% (37 of 51 patients) in the PRP group versus 51% (25 of 49 patients) in the corticosteroid group noted improved Disability of Arm, Shoulder, and Hand scores at 1 year ($P = .005$). Patients who received PRP also continued to report symptom relief 1 year after receiving the injection, whereas the short-term benefits of corticosteroids began to wane after 12 weeks. The improvement within this group of patients who received PRP continued to be noted 2 years after the PRP injection.[17]

- Summary and Recommendations: PRP is an effective treatment for lateral epicondylitis, with high-quality evidence demonstrating short-term and long-term efficacy. This recommendation also has been supported by previous reviews[42,44,45] and best available evidence specifically suggests LR-PRP should be the treatment of choice.

Patellar Tendinopathy

Results from randomized controlled trials (RCTs) appear to support the use of LR-PRP to treat chronic refractory patellar tendinopathy. Dragoo and colleagues[25] evaluated

Table 2
Study design characteristics for PRP versus control injection for tendinopathies

Indication	Study and Year of Publication	Level of Evidence	Sample Size		Type of PRP	Number of Injections	Intervention/Injection Volume and Contents		Follow-up, mo	Favors PRP?
			PRP	Control			PRP	Control		
Achilles tendinopathy	Boesen et al,[12] 2017	I	20	20	LP-PRP	4	4 mL PRP + eccentric training	Sham injection + eccentric training	6	+
Achilles Tendinopathy	de Jonge et al,[13] 2011	I	27	27	LR-PRP	1	4 mL PRP	4 mL normal saline	12	–
Achilles tendinopathy	Krogh et al,[14] 2016	I	12	12	LR-PRP	1	10–15 mL lidocaine → 6 mL PRP	10–15 mL lidocaine → 6 mL normal saline	3	–
Lateral epicondylitis	Behera et al,[15] 2015	I	15	10	LP-PRP	1	3 mL PRP + .5 mL calcium chloride	3 mL bupivacaine + 0.5 mL normal saline	12	+
Lateral epicondylitis	Gautam et al,[16] 2015	I	15	15	LP-PRP	1	2 mL PRP	2 mL methylprednisolone	6	+
Lateral epicondylitis	Gosens et al,[17] 2011	I	51	49	LR-PRP	1	3 mL PRP	3 mL triamcinolone	24	+
Lateral epicondylitis	Krogh et al,[18] 2013	I	20	20	LR-PRP	1	10–15 mL lidocaine → 3 mL PRP	10–15 mL lidocaine → 1 mL triamcinolone + 2 mL lidocaine	3	–
Lateral epicondylitis	Lebiedzinski et al,[19] 2015	I	64	56	LP-PRP	1	3 mL PRP	1 mL betamethasone + 2 mL lidocaine	12	+
Lateral epicondylitis	Mishra et al,[20] 2013	II	112	113	LR-PRP	1	Bupivacaine → 2–3 mL PRP	Bupivacaine → 2–3 mL bupivacaine	6	+
Lateral epicondylitis	Montalvan et al,[21] 2016	I	25	25	LP-PRP	2	2 mL lidocaine → 2 mL PRP	2 mL lidocaine → 2 mL normal saline	12	–
Lateral epicondylitis	Palacio et al,[22] 2016	I	20	20	LP-PRP	1	3 mL PRP	3 mL dexamethasone	6	–
Lateral epicondylitis	Stenhouse et al,[23] 2013	I	15	13	LP-PRP	2	1–2 mL lidocaine → 2 mL PRP	1–2 mL lidocaine	6	–

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Table 2
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Indication	Study and Year of Publication	Level of Evidence	Sample Size		Type of PRP	Number of Injections	Intervention/Injection Volume and Contents		Follow-up, mo	Favors PRP?
			PRP	Control			PRP	Control		
Lateral epicondylitis	Yadav et al,[24] 2015	I	30	30	LR-PRP	1	1 mL PRP	1 mL methylprednisolone	3	+
Patellar tendinopathy	Dragoo et al,[25] 2014	I	10	13	LR-PRP	1	3 mL bupivacaine → 6 mL PRP + dry needling	3 mL bupivacaine + dry needling	6	+
Patellar tendinopathy	Vetrano et al,[26] 2013	I	23	23	NR	2	2 mL PRP	Extracorporeal shock wave therapy	12	+
Plantar fasciitis	Acosta-Olivo et al,[27] 2016	I	14	14	NR	1	3 mL of PRP + .45 mL of 10% calcium gluconate + lidocaine	2 mL dexamethasone + 2 mL of lidocaine	4	–
Plantar fasciitis	Aksahin et al,[28] 2012	II	30	30	LR-PRP	1	3 mL PRP + 2 mL prilocaine	2 mL methylprednisolone + 2 mL prilocaine	6	–
Plantar fasciitis	Jain et al,[29] 2015	I	30	30	LR-PRP	1	2.5 mL PRP	1 mL triamcinolone + levobupivacaine + sodium bicarbonate	12	–
Plantar fasciitis	Jain et al,[30] 2018	II	40	40	LR-PRP	1	2 mL lidocaine → 3 mL PRP	2 mL methylprednisolone + 2 mL lidocaine	6	–
Plantar fasciitis	Mahindra et al,[31] 2016	I	25	25	NR	1	2.5–3 mL PRP	2 mL methylprednisolone	3	+
Plantar fasciitis	Monto,[32] 2014	I	20	20	LR-PRP	1	3 mL PRP + 6 mL bupivacaine	1 mL methylprednisolone + 6 mL bupivacaine	24	+
Plantar fasciitis	Omar et al,[33] 2012	II	15	15	NR	1	NR PRP	NR corticosteroid	1	+
Plantar fasciitis	Say et al,[34] 2014	II	25	25	NR	1	2.5 mL of PRP + 5.5% calcium chloride	1 mL methylprednisolone + 1 mL of prilocaine	6	+

Plantar fasciitis	Sherpy et al,[35] 2015	I	25	25	LR-PRP	1	PRP + mepivacaine	1 mL triamcinolone + mepivacaine	3	–
Plantar fasciitis	Shetty et al,[36] 2014	II	30	30	LR-PRP	1	8 mL PRP	1 mL triamcinolone + 3 mL lidocaine	3	+
Plantar fasciitis	Tiwari et al,[37] 2013	I	30	30	LR-PRP	1	5 mL PRP	1 mL methylprednisolone + 1 mL prilocaine	6	+
Plantar fasciitis	Vahdatpour et al,[38] 2016	I	16	16	LR-PRP	1	3 mL PRP	1 mL methylprednisolone + 1 mL lidocaine	6	+
Rotator cuff tendinopathy	Kesikburun et al,[39] 2013	I	20	20	LR-PRP	1	1 mL lidocaine → 5 mL PRP	1 mL lidocaine → 5 mL normal saline	12	–
Rotator cuff tendinopathy	Rha et al,[40] 2013	I	20	19	LR-PRP	2	<1 mL lidocaine → 3 mL PRP	<1 mL lidocaine	6	+
Rotator cuff tendinopathy	Shams et al,[41] 2016	I	20	20	LP-PRP	1	2–2.5 mL PRP	5 mL triamcinolone	6	–

Abbreviations: →, denotes sequential injection; LP-PRP, leukocyte-poor PRP; LR-PRP, leukocyte-rich PRP; NR, not reported; PRP, platelet-rich plasma. +, indicates that the trial found in favor of PRP; -, indicates the trial did not favor of PRP.

23 patients with patellar tendinopathy on examination and MRI who had failed conservative management. Patients were randomized to receive ultrasound-guided dry needling alone or with injection of LR-PRP. Patients were followed for more than 26 weeks. At 12 weeks, the PRP group had improved, as measured by Victorian Institute of Sports Assessment, Patellar Tendon (VISA-P) score, significantly more than the dry needling group ($P = .02$). However, the difference was not significant at more than 26 weeks ($P = .66$), suggesting that the benefit of PRP for patellar tendinopathy may be *earlier* improvement of symptoms. Vetrano and colleagues[26] also reported the benefit of PRP injections for treatment of chronic refractory patellar tendinopathy. Forty-six patients with ultrasound-confirmed chronic unilateral patellar tendinopathy were randomized to receive either 2 PRP injections over 2 weeks or 3 sessions of focused extracorporeal shock wave therapy (ECSWT). Although there was no significant difference between groups at 2-month follow-up, the PRP group showed statistically significant improvement, as measured by VISA-P and VAS, over ECSWT at 6-month and 12-month follow-up, and as measured by Blazina scale score at 12-month follow-up ($P<.05$ for all).

- Summary and Recommendations: A small amount of high-quality evidence supports the use of PRP in chronic refractory patellar tendinopathy and LR-PRP is recommended. Given the small number of studies supporting this conclusion, further clinical trials will help make this suggestion more robust.

Achilles Tendinopathy

In a prospective randomized trial, de Vos and colleagues[46,47] found no significant benefits with LR-PRP versus a saline solution injection as an adjunct to eccentric exercises for mid-Achilles tendinosis. The investigators reported no significant differences in Achilles tendon structure, the degree of neovascularization, and clinical outcome compared with the saline solution group. In a follow-up study on the same patients, de Jonge and colleagues[13] similarly reported no significant benefit in terms of pain reduction, activity level, and tendon appearance on ultrasound at 1 year after injection of PRP for chronic Achilles tendinopathy. A more recent RCT by Boesen and colleagues[12] compared 4 LP-PRP injections each 14 days apart against sham injection with a few drops of subcutaneous saline. All participants performed eccentric Achilles training and the group treated with PRP had significantly improved pain, function, and activity scores at all time points throughout the 6-month follow-up period compared with sham injection. Of note, however, this study also found a comparable improvement with a single high-volume injection (50 mL) of 0.5% bupivacaine (10 mL), methylprednisolone (20 mg), and normal saline (40 mL).

- Summary and Recommendations: Evidence for the use of PRP in Achilles tendinopathy is mixed at best, and therefore routine use of PRP in Achilles tendinopathy is not supported by current literature. As stated, one clinical trial[12] reported efficacy of 4 LP-PRP injections, but also found similar results for high-volume injection of anesthetic, corticosteroid, and saline, perhaps suggesting the benefit may be due to mechanical volume effects.

Rotator Cuff Tendinopathy

Few high-level RCTs have analyzed PRP as a conservative management strategy for rotator cuff pathology. Kesikburun and colleagues[39] looked at subacromial PRP injections in patients with chronic rotator cuff pathology (pain >3 months, with MRI confirming pathology, and >50% relief with subacromial anesthetic injection). The study found no difference in its patient-reported outcome scores when compared with a placebo

subacromial injection of saline. In contrast, in an RCT, Rha and colleagues[40] demonstrated significant improvements in pain following 2 injections of LR-PRP 4 weeks apart compared with placebo. Shams and colleagues[41] reported comparable improvements between subacromial PRP and corticosteroid injection in Western Ontario Rotator Cuff Index, Shoulder Pain Disability Index, and VAS shoulder pain with Neer test.

- Summary and Recommendations: Although there remains a paucity of evidence to routinely recommend PRP injections for rotator cuff tendinopathy, PRP may be a safe and effective alternative to corticosteroid injections in conservative treatment of rotator cuff tendinopathy.

Plantar Fasciitis

Several RCTs have evaluated PRP injection in the management of chronic plantar fasciitis. Although the current standard injection therapy following failure of more conservative management has been a local injection of corticosteroid, it often requires multiple injections that can be associated with fat pad atrophy or plantar fascia rupture.[48] The potential of PRP as a local injection treatment mitigates these concerns. Two recent meta-analyses[49,50] evaluated PRP injections against corticosteroid injections, concluding that PRP injections were a viable alternative to corticosteroid injections with respect to efficacy, with some studies demonstrating superiority of PRP.[31–34,36–38] Given the small sample sizes and limited number of high-quality RCTs, larger-scale high-quality RCTs with more extensive follow-up will be warranted.

- Summary and Recommendations: PRP injections are an effective treatment for improving pain and function in chronic plantar fasciitis and may be superior to corticosteroids, especially considering the complications of multiple corticosteroid injections that are not associated with PRP.

OSTEOARTHRITIS

When considering biologic approaches to cartilage pathology, it is important to understand that osteoarthritis (OA) has unique characteristics with respect to joint biology, homeostasis, and levels of metalloproteases and inflammatory cytokines.[51] The idea of using PRP for cartilage regeneration is based on in vitro basic science literature that suggests that growth factors released by the platelet alpha granules may increase the synthetic capacity of chondrocytes through upregulation of gene expression, proteoglycan production, and deposition of type II collagen.[52–54] Clinical reports on the use of PRP for cartilage injury have involved patients with OA of the knee or hip (**Table 3**).

Osteoarthritis of the Knee

There have been a large volume of studies assessing the efficacy of intra-articular PRP injections for OA of the knee. PRP has been compared against placebo, other alternative injections (corticosteroid, hyaluronic acid [HA]), oral medication (Tylenol 500 mg every 8 hours), homeopathic treatments (ozone therapy), and lifestyle changes.[74] Shen and colleagues[75] performed a meta-analysis looking at 14 RCTs comprising 1423 patients. Individual RCTs had different preparations of PRP including LR-PRP, LP-PRP, and plasma rich in growth factor (PRGF) Endoret.[75] The meta-analysis demonstrated that multiple injections of PRP showed significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 3-month, 6-month, and 12-month follow-ups when compared with the controls (P = .02, .004, < .001, respectively), and PRP did not show increased risk of

Table 3
Study design characteristics for PRP versus control injection for osteoarthritis

Indication	Study and Year of Publication	Level of Evidence	Sample Size		Type of PRP	Number of Injections	Intervention/Injection Volume and Contents		Follow-up, mo	Favors PRP?
			PRP	Control			PRP	Control		
Hip OA	Battaglia et al,[55] 2013	I	50	50	LR-PRP	3	5 mL PRP	30 mg HA	12	–
Hip OA	Dallari et al,[56] 2016	I	44, +HA:31	36	NR	3	7 mL PRP + HA	30 mg HA	12	+
Hip OA	Doria et al,[57] 2017	II	40	40	NR	3	5 mL PRP	15 mg HA	12	–
Hip OA	Sante et al,[58] 2016	I	21	22	NR	3	3 mL PRP	30 mg HA	4	+
Knee OA	Cerza et al,[59] 2012	I	60	60	LP-PRP	4	5.5 mL PRP	20 mg HA	4	+
Knee OA	Cole et al,[60] 2017	I	49	50	LP-PRP	3	4 mL PRP	16 mg HA injection	12	+
Knee OA	Duymus et al,[61] 2017	I	41	HA:40, Ozone:39	NR	2	5 mL PRP	40 mg HA, 15 mL ozone	12	+
Knee OA	Filardo et al,[62] 2015	I	96	96	LR-PRP	3	5 mL PRP	30 mg HA	12	–
Knee OA	Filardo et al,[63] 2012	I	54	55	LR-PRP	3	5 mL PRP	NR HA	12	–
Knee OA	Gormeli et al,[64] 2017	I	PRP(3x):46 PRP(1x):45	HA:46, Placebo:45	NR	3 vs 1	5 mL PRP	30 mg HA, NR saline	6	+
Knee OA	Lana et al,[65] 2016	I	36, +HA: 33	36	NR	3	5 mL PRP + 20 mg HA	20 mg HA	12	+
Knee OA	Montanez et al,[66] 2016	I	28	27	NR	3	NR	NR HA	6	+

Knee OA	Patel et al,[67] 2013	I	PRP1:27 PRP2:25	Placebo:26	LP-PRP	1 vs 2	8 mL PRP	8 mL Saline	6	+
Knee OA	Paterson et al,[68] 2016	I	12	11	NR	3	3 mL PRP	3 mL HA	3	–
Knee OA	Raeissadat et al,[69] 2015	I	87	73	LR-PRP	2	4–6 mL PRP	20 mg HA	12	+
Knee OA	Rayegani et al,[70] 2014	I	31	31	LR-PRP	2	4–6 mL PRP + therapeutic exercise	Therapeutic exercise alone	6	+
Knee OA	Sanchez et al,[71] 2012	I	89	87	LP-PRP	3	8 mL PRGF	NR HA	6	+
Knee OA	Simental et al,[72] 2016	I	33	32	LP-PRP	3	3 mL PRP	Tylenol 500 mg q8h	4	+
Knee OA	Smith et al,[73] 2016	I	15	15	LP-PRP	3	3–8 mL PRP	3–8 mL Saline	12	+
Knee OA	Vaquerizao et al,[74] 2013	I	48	48	LP-PRP	3	8 mL PRGF	NR HA	11	+

Abbreviations: HA, hyaluronic acid; LP-PRP, leukocyte-poor PRP; LR-PRP, leukocyte-rich PRP; NR, not reported; OA, osteoarthritis; PRGF, plasma rich in growth factors.

postinjection adverse effects (Relative risk 1.40; 95% confidence interval 0.80–2/40; $I^2 = 59\%$; $P = .24$).[75] They concluded that intra-articular PRP injections are more efficacious in the treatment of knee OA with respect to pain relief and patient-reported outcomes versus other alternative injections.

In the various individual studies within that meta-analysis, it was shown that many subjects who underwent intra-articular injections of PRP reported pain relief compared with baseline. On subgroup analysis examining the efficacy of PRP-based severity of knee OA, PRP was shown more effective in patients with mild to moderate OA.[59,61,64–66,68,69,71] However, a few studies demonstrated no difference in WOMAC scores when compared with HA injection,[60,62,63,67] whereas other studies showed diminishing results in pain relief and function after a certain amount of time.[68] One possible explanation for this discrepancy is the heterogeneity of the PRP preparations and regimens being evaluated for OA of the knee.

A meta-analysis by Riboh and colleagues[76] compared LP-PRP and LR-PRP in the treatment of knee osteoarthritis and found that LP-PRP injections resulted in significantly improved WOMAC scores compared with HA[59,71] or placebo.[67,77] Patel and colleagues[67] performed a prospective randomized trial comparing single-injection or double-injection LP-PRP with saline solution in 78 patients with early OA. They concluded that a single injection of PRP was as effective as a double injection. On the other hand, Filardo and colleagues[62] enrolled 192 patients in a randomized controlled study and found no difference between LR-PRP and HA, providing further evidence that LP-PRP may be an effective choice for treatment of OA symptoms, whereas LR-PRP appears not to be.[76] The biological basis for this may be in the relative level of inflammatory versus anti-inflammatory mediators present in LR-PRP and LP-PRP. Inflammatory mediators TNF-α, IL-6, interferon-Υ, and IL-1β are increased significantly in the presence of LR-PRP,[10,78,79] whereas injection of LP-PRP increases IL-4 and IL-10, which are anti-inflammatory mediators. IL-10 specifically was found to be helpful in the treatment of hip OA,[56] and may also suppress the release of the inflammatory mediators TNF-α, IL-6, and IL-1β, and block the inflammatory pathway by neutralizing nuclear factor–kB activity.[10,56,70,72,78] In addition to its deleterious effects on chondrocytes, LR-PRP may also fail to help treat OA symptoms due to its effect on synoviocytes. Braun and colleagues[80] found that treatment of synovial cells with LR-PRP or erythrocytes resulted in significant proinflammatory mediator production and cell death.

- Summary and Recommendations: Intra-articular injection of LP-PRP is a safe treatment option for knee OA, and many RCTs have demonstrated its ability to reduce pain symptoms and increase.[73,75] Larger studies with longer follow-up need to be done to characterize its long-term efficacy.

Osteoarthritis of the Hip

Compared with knee OA, studies on the effects of PRP for hip OA have been limited, with 4 RCTs (to date) comparing PRP injections for OA of the hip with HA injections. Battaglia and colleagues[55] compared clinical efficacy of PRP and HA injections in 100 patients with chronic symptomatic hip OA. Patients were randomized to the 2 groups, and VAS and Harris Hip Score (HHS) outcomes were measured at baseline and at 1, 3, 6, and 12 months. Both PRP and HA injections demonstrated significant improvement at all time points with peak improvement at 3 months, and gradual diminishing effects thereafter to 12 months. The outcome scores at 12 months still displayed significant improvement when compared with baseline ($P<.0005$)[55]; however, there was no statistically significant difference between PRP and HA treatment groups.

Di Sante and colleagues[58] looked at 43 patients with severe hip OA who were randomized to receive either an intra-articular PRP injection or an intra-articular HA injection. Outcomes were measured using the VAS and WOMAC pain scores at baseline, 4 weeks, and 16 weeks following treatment. In the PRP group, VAS scores significantly decreased at 4 weeks but not at 16, suggesting an initial, but not sustained reduction in pain. Interestingly, the HA group saw a significant difference at week 16, but not week 4 when compared with baseline.[58]

Dallari and colleagues[56] evaluated PRP against HA injections for hip OA, and also compared the combination of HA and PRP injected together to both injections alone. The PRP group was found to have the lowest VAS score of all 3 groups at all follow-up periods (2 months, 6 months, and 12 month). The PRP group also had a significantly better WOMAC score at 2 and 6 months, but not at 12 months. In a different study, Doria and colleagues[57] performed a double-blind RCT comparing patients who received 3 consecutive weekly injections of PRP versus 3 HA injections. The study showed no significant difference between the PRP and HA groups, but both groups showed improved HHS, WOMAC, and VAS scores at 6 and 12 months following treatment. None of the studies showed an adverse effect from intra-articular PRP injections into the hip and all concluded that PRP was safe.

Overall, although limited data, intra-articular injection of PRP for hip OA has been shown to be safe and have some efficacy in pain reduction and function as measured by patient-reported outcome scores. Multiple studies have shown PRP to initially have a better pain reduction when compared with HA; however, that initial advantage seems to decrease over time with PRP and HA having very similar efficacy by 12 months.

- Summary and Recommendations: PRP may have some efficacy for early and temporal pain relief in hip OA and overall had very similar efficacy as HA injections. As there have been a small number of clinical studies evaluating the use of PRP for OA of the hip, more level I evidence is needed to determine if PRP can be used as an alternative conservative treatment to delay surgery for OA of the hip.

SURGICAL AUGMENTATION

Rotator Cuff Repair

Several high-level clinical studies have evaluated the use of PRP products as augmentations in arthroscopic repair of rotator cuff tears (**Table 4**). Many of the studies have specifically analyzed the use of platelet-rich fibrin matrix preparation for augmentation (PRFM),[81,82,90,91,93] whereas other studies analyzed the use of injected PRP directly into the repair site.[87,89,94] There is, however, significant heterogeneity of the PRP or PRFM preparations in these studies. Results were obtained with patient-directed outcomes, most commonly University of California–Los Angeles (UCLA), American Shoulder and Elbow Society (ASES) and Constant Shoulder scores, Simple Shoulder Test (SST) scores, and VAS pain scores. Some studies have also used imaging, such as ultrasound and MRI, to measure differences in tendon healing, healing time, and retear rates. Objective clinical data, such as rotator cuff strength and shoulder range of motion (ROM) have also been collected to measure functional outcome differences.[39,84,86,87,91] Most of the data have shown little utility for PRP in rotator cuff tendinopathy or as augmentation in arthroscopic rotator cuff repair.[39,82,83,86,88–91,93,95,96] However, limited data have shown some effect in reducing perioperative pain.[41,86,89,95]

Saltzman and colleagues[97] and Filardo and colleagues[98] performed large meta-analyses, and showed that PRP had no significant benefit in augmentation of

Table 4
Study design characteristics of surgical augmentation with PRP in rotator cuff repair

Indication	Study and Year of Publication	Level of Evidence	Sample Size		Type of PRP	Number of Injections	Intervention/Injection Volume and Contents		Follow-up, mo	Favors PRP?
			PRP	Control			PRP	Control		
Rotator cuff repair	Bergeson et al,[81] 2012	III	16	21	PRFM	1	PRFM + single-row or double-row repair	Single-row or double-row repair	12	–
Rotator cuff repair	Castricini et al,[82] 2011	I	43	45	NR-PRFM	1	PRFM + double-row repair	Double-row repair	16	–
Rotator cuff repair	D'Ambrosi et al,[83] 2016	I	20	20	NR	1	16 mL PRP + single-row repair	Single-row repair	6	+
Rotator cuff repair	Ebert et al,[84] 2017	I	30	30	LP-PRP	2 (day 7 and 14)	2–4 mL PRP + double-row repair	Double-row repair	42	+
Rotator cuff repair	Gumina et al,[85] 2012	I	39	37	LR-PRFM	1	PRFM + single-row repair	Single-row repair	12	–
Rotator cuff repair	Holtby et al,[86] 2016	I	41	41	LP-PRP	1	7 mL PRP + single-row repair	Single-row repair	6	–
Rotator cuff repair	Jo et al,[87] 2015	I	37	37	LP-PRP	3	3 mL PRP gel + double-row repair	Double-row repair	12	+
Rotator cuff repair	Malavolta et al,[88] 2014	I	27	27	LR-PRP	1	20 mL PRP + single-row repair	Single-row repair	24	–
Rotator cuff repair	Randelli et al,[89] 2011	I	26	27	LR-PRP	1	6 mL PRP + single-row repair	Single-row repair	24	+
Rotator cuff repair	Rodeo et al,[90] 2012	II	40	39	PRFM	1	PRFM + single-row or double-row repair	Single-row or double-row repair	12	–
Rotator cuff repair	Weber et al,[91] 2013	I	30	30	LP-PRFM	1	PRFM clot + single-row repair	Single-row repair	12	–
Rotator cuff repair	Zumstein et al,[92] 2016	I	17	18	LR-PRFM	1	PRFM + double-row repair	Double-row repair	12	–

Abbreviations: LP-PRP, leukocyte-poor PRP; LR-PRP, leukocyte-rich PRP; NR, not reported; PRFM, platelet-rich fibrin matrix. +, indicates that the trial found in favor of PRP; -, indicates the trial did not favor of PRP.

arthroscopically repaired rotator cuffs. Saltzman and colleagues[97] looked at 7 meta-analyses encompassing a total of 3193 patients. At mean follow-up of 12 to 21 months, no significant difference was found when compared with controls in 5 of 6 studies measuring constant scores, 6 of 6 measuring UCLA scores, 4 of 5 measuring ASES scores, and 3 of 5 measuring SST scores. However, a subgroup analysis did see a trend toward better outcomes with PRP in the form of PRFM; in the treatment of small and medium tears versus large/massive tears; when applied to the tendon-bone interface versus over the tendon; and when applied with double-row versus single-row rotator cuff repairs.[97]

Vavken and colleagues[99] performed a meta-analysis of 14 studies looking at PRP-augmented rotator cuff repairs. They were divided into subgroups of small and medium tears (<3 cm) and large tears (>3 cm). In large tears, there were no beneficial effects of PRP-augmented surgery. In small and medium tears, there was a beneficial effect of reducing retear rates ($P = .038$).

Some individual studies have determined a utility for PRP in different tear sizes and patterns. Cai and colleagues[96] found PRP augmentation to be associated with a lower failure to heal rate in small to moderate tears. Jo and colleagues[87] found that PRP application with medium and large tear repairs led to a decrease in retear rates (3% vs 20% in the conventional group) and an increased cross-sectional area of the supraspinatus on follow-up MRI when compared with no augmentation. Potentially due to the anti-inflammatory properties of PRP, PRP application has been shown to reduce pain in the early postoperative period following surgery.[83,86,89] Flury and colleagues[95] showed similar pain reduction when compared with an injection of ropivacaine.

- Summary and Recommendations: Evidence from randomized clinical trials and large meta-analyses do not demonstrate an absolute benefit of PRP augmentation in rotator cuff repair surgery. A recent critical analysis review[100] reached a similar conclusion that PRP could not be routinely recommended as an augmentation in rotator cuff repair, but that activated PRFM delivered at the bone-tendon interface in conjunction with double-row repair technique had the best results in subgroup analyses. Some limited data have shown PRP may be useful in reducing postoperative pain and repair of small and medium tears.

Achilles Tendon Repair

The effects of PRP to augment healing in Achilles tendon ruptures have been promising in preclinical models. Most studies in rodents show a beneficial effect of platelets on the healing of acute Achilles tendon ruptures when used as an adjunctive therapy.[101–108] Caution is warranted, however, when extrapolating results from preclinical Achilles rupture models to human patients,[109] due to the difference in the size of the tendons between species, which has significant effects in terms of diffusion and cellular migration distances.[110] Furthermore, rodents tend to load their healing Achilles tendons to a greater extent than humans, which leads to more favorable biomechanical outcomes.[111]

Clinical trials in humans are limited with respect to the use of PRP in the repair of acute Achilles tendon tears, and their findings are somewhat conflicting. Schepull and colleagues[112] evaluated the use of PRP in Achilles tendon repair in a randomized study (n = 30) in which PRP was injected into the injury site at the time of primary suture repair. Although no differences were reported with regard to tendon elasticity and heel raise index between the PRP and control groups, the investigators did note a lower Achilles Tendon Total Rupture score among the PRP group, which suggests a detrimental effect of PRP on subjective outcome after repair. Additionally, another study

also demonstrated equivalence in structural and functional results in patients with Achilles tendon ruptures surgically treated with and without addition of PRP.[113] However, Zou and colleagues[114] enrolled 36 patients with acute Achilles tendon rupture in a prospective randomized controlled study using intraoperative LR-PRP injection versus repair without PRP. Patients were followed for 24 months. Patients from the PRP group had better isokinetic muscle at 3 months and had higher SF-36 and Leppilahti scores at 6 and 12 months, respectively ($P<.05$ for all). Ankle ROM was also significantly better in the PRP group at all time points of 6, 12, and 24 months ($P<.001$).

- Summary and Recommendations: Injection of PRP is not definitively beneficial as a surgical augmentation for acute Achilles tendon repair, although the available literature is conflicting.

Anterior Cruciate Ligament Surgery

The success of anterior cruciate ligament (ACL) surgery not only hinges on technical factors (eg, graft-tunnel placement and graft fixation) but also biologic healing of the ACL graft. Studies on the use of PRP in ACL reconstruction surgery have focused on 3 biologic processes: (1) osteoligamentous integration of the graft into the tibial and femoral tunnels, (2) maturation of the articular portion of the graft, (3) and graft harvest site healing and pain reduction.[115] Within the literature, ACL graft maturation tends to be assessed with MRI. The assumption is that a low homogeneous intensity signal on T2-weighted and proton density–weighted MRI is likely indicative of a healthy maturing ACL graft. In terms of the effect of PRP on ACL graft maturation, some studies have demonstrated improved graft maturation with PRP,[116–119] whereas others report no significant differences.[120,121] The investigators of a recent systematic review of 11 controlled trials, which included studies in which statistical significance was not reached, concluded that PRP likely improves ACL graft maturation by up to 50%. The investigators pointed to insufficient sample size as a potential rationale for lack of statistical significance despite MRI improvement in some metrics measuring ACL graft maturation.[122]

The other component to successful biologic healing of an ACL graft is graft–bone tunnel incorporation. Recent data on the use of PRP to augment healing of the graft-bone interface has shown no clinical benefit of PRP in tunnel widening or osteointegration of the graft.[120,123] Vogrin and colleagues[121] evaluated the effects of PRP gel treatment for hamstring autograft ACL reconstruction in a controlled, double-blind study. The investigators reported MRI evidence of improved vascularization along the ACL graft-bone interface at 3 months with use of PRP, but the observed benefit dissipated by 6 months after surgery. Other studies have similarly reported limited to no evidence to support the use of PRP to augment ACL graft–bone tunnel incorporation.[116,124] Of note is that nearly all of the studies used an LR-PRP formulation, and LR-PRP formulations increase local tissue inflammation, which may delay or alter healing.[8]

One final point of consideration is whether any of the observed benefit of PRP on ACL graft maturation or graft-tunnel healing would translate into improved clinical results. The best available evidence seems to suggest no significant benefit for functional outcomes with PRP augmentation.[116,120,125] Ventura and colleagues[125] found no differences in knee injury and osteoarthritis outcome score (KOOS) scores, Tegner scores, or KT-1000 measurements between the PRP-treated group and control subjects at 6 months after surgery, despite reporting a significant difference in graft appearance. Orrego and colleagues[116] similarly noted no significant benefit in both Lysholm and International Knee Documentation Committee (IKDC) scores at 6 months after surgery, despite identifying a positive effect of PRP on graft maturation. Current

literature suggests that PRP may improve the rate at which ACL grafts achieve a low signal on MRI T2-weighted imaging, but likely has little to no effect on graft-tunnel incorporation. A demonstrable benefit in patient outcome after use of PRP in patients undergoing ACL surgery is also lacking.

Other clinical trials have assessed the impact of PRP on donor site (graft harvest site) pain and healing, with some promising early results. De Almeida and colleagues[126] looked at adding PRP to the patellar tendon harvest site and measuring patient-reported pain scores and patellar tending gapping on MRI at 6 months following surgery. The investigators found that patients reported better immediate postoperative pain scores, and at 6 months there was significantly less gapping on MRI, although isokinetic testing results were no different.[126] Seijas and colleagues[127] looked at anterior knee pain after bone-patellar-bone autograft ACL reconstruction with PRP application, and found decreased anterior knee pain when compared with controls. In a different study, Cervellin and colleagues[128] did not see a significant difference in VAS pain scores, but found that the PRP group had a significantly higher VISA score.

- Summary and Recommendations: More studies are needed to investigate the effect of PRP on ACL graft integration, maturation, and donor site pain. Early studies have shown no significant clinical effect of PRP on graft integration or maturation, but newer studies have shown promising results in decreasing donor site pain.

ANKLE SPRAINS

There are very little high-level data analyzing PRP injections in ankle sprains, with (to date) 2 published RCTs available. Rowden and colleagues[129] performed a double-blinded placebo-controlled randomized clinical trial of patients with acute ankle sprains in the emergency room comparing ultrasound-guided LR-PRP injections with local anesthetic versus injection of normal saline with local anesthetic. Injections were performed adjacent to an injured ligament if visualized on ultrasound or otherwise were injected into the site of maximal tenderness. For all patients, a posterior splint was placed with non–weight-bearing restrictions for 3 days. Pain medication was given at the physician's discretion. Primary outcome measures were VAS pain score and Lower Extremity Functional Sale (LEFS) on day 0 (baseline), day 3, and day 8. The investigators found that there was no statistical difference in the VAS pain score or LEFS between the 2 groups.[1] Laver and colleagues[130] randomized 16 elite athletes diagnosed with high ankle sprains, including an injured anteroinferior tibiofibular ligament to treatment with either an ultrasound-guided LP-PRP injection at initial presentation with a repeat injection 7 days later in conjunction with a rehabilitation program, versus rehabilitation program alone. Primary outcomes were measured by return-to-play and dynamic imaging studies. All patients received the same rehabilitation protocol and return-to-play criteria. The study found the LP-PRP group returned to play in a shorter amount of time (40.8 days) compared with the control (59.6 days, $P<.006$).[130] Only 1 patient had residual pain after return to play in the PRP group, whereas 5 patients had residual pain in the control. No significant difference was seen in the dynamic imaging studies in external rotation between the 2 groups 6 weeks post injury.

- Summary and Recommendations: PRP has not been shown to be efficacious in the setting of acute ankle sprains, but limited evidence suggests that LP-PRP injections may be helpful in high ankle sprains to reduce return-to-play time and decrease incidence of residual pain in elite athletes. However, due to the limited amount of high-level evidence, the use of PRP injections cannot be routinely recommended for high ankle sprains.

MUSCLE INJURIES

The use of PRP in the treatment of muscle injuries has attracted a significant amount of interest in recent years. Similar to tendon healing, the steps in muscle healing involve the initial inflammatory response, which is followed by cell proliferation, differentiation, and tissue remodeling. Hamid and colleagues[131] conducted a single-blind randomized study of 28 patients with grade 2 hamstring muscle injuries comparing an injection of LR-PRP with a rehabilitation program, versus rehabilitation alone. The group treated with LR-PRP was able to return to play in a significantly shorter amount of time compared with controls (average 26.7 vs 42.5 days, $P = .02$), but structural improvement was not achieved. In a double-blind RCT, Reurink and colleagues[132] evaluated 80 patients comparing intramuscular PRP injections for the treatment of acute hamstring muscle injuries as diagnosed on MRI with placebo saline injections, with all patients receiving standard rehabilitation. The patients were followed for 6 months, and the investigators reported no significant differences between the groups in return-to-play time or in reinjury rates.

Although clinical studies have not found PRP to be efficacious in treating muscle injuries, basic science research may lead to an improved understanding of treatment modalities. In vitro work has found that PRP is capable of leading to myoblast proliferation, but not to myoblast differentiation,[133] a requisite step in producing muscle tissue. Furthermore, growth factors contained in platelets, specifically myostatin and TGF-β1, are actually detrimental to muscle regeneration.[134,135] Miroshnychenko and colleagues[136] found in vitro that treatment with PPP or PRP with a second spin to remove the platelets induced myoblasts into muscle differentiation. This suggests that perhaps the most beneficial treatment of muscle injuries may be with PPP, although in vivo animal studies followed by human clinical trials will be necessary to further explore this treatment option in the future.

- Summary and Recommendations: PRP injections have not been found to be an efficacious treatment modality in the treatment of muscle injuries in current clinical studies, but preclinical studies suggest that perhaps future clinical investigation into the use of PPP or PRP with platelets removed may be beneficial.

FRACTURE AND NONUNION MANAGEMENT

Most preclinical investigations favor the use of PRP to improve bone healing.[137,138] This is mainly due to accelerated and increased bone regeneration demonstrated in fracture models treated with PRP.[139–146] Additionally, PRP treatment has been shown to ameliorate bone strength in a rodent osteotomy model.[144] In isolation, however, PRP treatment alone does not effectively heal critical-sized bone defects.[147–149]

Despite the positive findings in the preclinical literature, there is no consensus to support the routine use of PRP to enhance bone healing based on high-quality clinical studies. To this point, a recent review of PRP and acute fracture treatment notes that 3 of the included RCTs failed to show benefit with respect to functional outcomes, whereas 2 of the included studies showed superior clinical outcomes.[138] Most trials in this review (6 of 8) studied efficacy of PRP when combined with other biologics, such as mesenchymal stem cells and/or bone graft, to promote fracture healing. In terms of nonunion treatment, there was only 1 RCT identified reporting clinical outcomes measures. This study failed to show a benefit of PRP when compared with bone morphogenetic protein 7 (which is standard of care) when treating tibia nonunions.[150]

- Summary and Recommendations: Current evidence does not support the use of PRP in acute fracture or nonunion management

SUMMARY OF RECOMMENDATIONS

PRP remains a promising treatment for musculoskeletal maladies, and clinical data to date have shown that PRP is safe. However, evidence of its efficacy has been mixed and highly variable depending on the specific indication. Additional future high-quality large clinical trials will be critical in shaping our perspective of this treatment option. The heterogeneity of PRP preparations, both presently and historically, leads sweeping recommendations about its utility impossible to make. This heterogeneity has also made interpreting existing literature more complicated. Nonetheless, based on the current best available literature, the following recommendations are summarized:

- There is abundant high-quality level I evidence to recommend LR-PRP injections for lateral epicondylitis and LP-PRP injections for OA of the knee
- There is a moderate amount of high-quality level I evidence to recommend LR-PRP injections for patellar tendinopathy and PRP injections for plantar fasciitis
- There is currently insufficient high-quality evidence for recommendation, but small clinical trials have shown promising efficacy for PRP injections for rotator cuff tendinopathy, OA of the hip, donor site pain in ACL reconstruction with patellar tendon autograft, and LP-PRP injections for high ankle sprains
- The best available clinical evidence does not demonstrate efficacy of PRP injections for Achilles tendinopathy, acute fracture, or nonunion; surgical augmentation with PRP in rotator cuff repair, Achilles tendon repair, and ACL reconstruction; and efficacy has not been shown with PRP injections for muscle injuries, although preclinical studies suggest PPP may hold promise for muscle injuries but clinical trials will be necessary to validate this.

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