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Platelet-rich plasma: a narrative review

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- The aim of this article was to synopsize platelet-rich plasma (PRP) use in musculoskeletal pathologies through evidence-based assessment of the preparation, classification, mechanism of action and applications of PRP, thereby answering which PRP type is best for each clinical indication.
- The literature search was performed using Medline, EMBASE and Cochrane Reviews databases for papers containing the key terms "platelet-rich plasma" AND "orthopaedics" AND ("classification" OR "mechanism of action" OR "preparation" OR "clinical application"). Generated papers were evaluated for pertinence in following areas: preparation, classification, mechanism of action, clinical application within orthopaedics. Non-English papers were excluded. Included studies were evaluated for quality.
- Sixty studies were included in our review. There are many commercial PRP preparation kits with differing component concentrations. There is no consensus on optimal component concentrations. Multiple PRP classifications exist but none have been validated. Platelet-rich plasma acts via growth factors (GFs) released from α-granules within platelets. Growth factors have been shown to be beneficial in healing. Grossly elevated concentrations of GFs may have inhibitory effects on healing. Multiple systematic reviews show efficacy of PRP in tendinopathies, early osteoarthritis, acute muscle injuries and in combination with rotator cuff repair and anterior cruciate ligament reconstruction.
- The literature suggests leukocyte-rich PRP (L-PRP) is more beneficial in tendinopathies and pure PRP (P-PRP) is more beneficial in cartilage pathology. However, different PRP preparations have not been directly compared in any pathology. Classification of PRP type is frequently not stated in research. Standardization of PRP research parameters is needed to streamline findings and generate clear indications for PRP types to yield maximum clinical benefit.

Keywords: orthopaedics; osteoarthritis; platelet-rich plasma; soft tissue; sports and exercise medicine

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Introduction

Arthritis and soft tissue pathology make up the majority of orthopaedic referrals. An increasing proportion of patients are developing these pathologies at an earlier age, thereby producing a growing societal cost on healthcare and reduced productivity.[1–4] This has led the drive to find treatments that can delay, or preferably cure, diagnoses that would otherwise require surgical intervention at an age or time when it would not typically be undertaken.

Platelet-rich plasma (PRP) is an autologous blood product acquired from part of the plasma fraction created via centrifugation of whole blood. By definition it has a platelet concentration above that of normal physiological levels.[5]

The term PRP originated in the 1970s by haematologists describing plasma with a platelet count higher than peripheral blood,[6] which at the time was being used as a transfusion product in thrombocytopaenic patients.[5] Since then it has been applied in multiple fields including plastic surgery, paediatric surgery, cardiac surgery, gynaecology, urology and ophthalmology.[7] However, it is within the musculoskeletal field where there has been a surge of PRP use for multiple pathologies, largely due to widespread commercial interest following PRP use in professional sport.[8]

This review aims to synopsise PRP use in musculoskeletal pathologies through evidence-based assessment of the preparation, classification systems, mechanism of action and clinical applications of PRP and thereby answer, 'What type of PRP is best for different clinical indications?' We attempt to interpret the current viability of PRP within orthopaedics to help direct the focus of future research.

Methods

A literature search was performed using the Medline, EMBASE and Cochrane Reviews databases for all papers published between 1978 and 2019 containing the following key terms: "platelet-rich plasma" AND "orthopaedics" AND ("classification" OR "mechanism of action" OR "preparation" OR "clinical application").

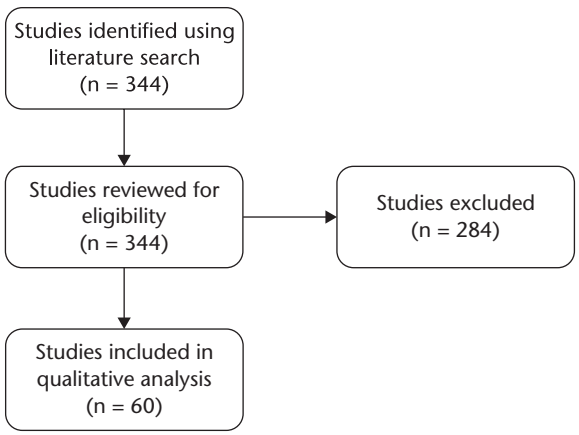


Fig. 1 Study flow diagram.

Selection criteria

Yielded papers were evaluated independently by two authors and selected if containing pertinence to PRP regarding one or more of the following areas: preparation, classification, mechanism of action, or clinical application within trauma and orthopaedics. Papers not written in English and animal studies relating to applications were excluded. The authors acknowledge an element of language bias; however, using more modern publications limits the extent of exclusion.

Literature grading and analysis

Studies were independently rated by two authors using the Oxford Centre for Evidence-based Medicine 'Levels of evidence' document[9] and the Coleman modified score (CMS) when applicable.

Results

Sixty studies[5,10–68] were included in our analysis published between 1978 and 2019. Details of the literature search and data extraction can be seen in a flow diagram (Fig. 1).

Preparations

Platelet-rich plasma can be formulated in multiple ways with no consensus on a definitive protocol that could be used internationally to standardize the formulation. The following section is based on level 5 evidence surrounding the preparation of PRP. The basis of the preparations relies on the concept of differential centrifugation.[10] Each component of whole blood has a different specific gravity and, when spun in a centrifuge, separates into distinct layers.

There are two principle methods of producing PRP, the PRP method and the buffy-coat method.[10] The PRP method uses fresh blood from venepuncture, which is placed in a centrifuge for a 'soft' spin to separate the red blood cells (RBCs). The supernatant plasma is then centrifuged in a 'hard' spin at higher speeds to obtain the platelet concentrate. The buffy-coat technique utilizes whole blood, prestored at room temperature (i.e. 20–24°C). It undergoes a 'hard' spin to separate it into three layers: RBCs, platelets and white blood cells (WBCs), and platelet-poor plasma. The supernatant plasma is removed, and the buffy-coat is separated. This layer undergoes a second low-speed spin to separate the WBCs, or a leukocyte filter can be used.

Centrifugation rate has proved important in determining the optimal platelet yield. Most PRP production involves two spins – for separation and then concentration; the main factors of these spins are the speed in rotations per minute (RPM) and duration. Sabarish et al[11] studied three differing protocols involving spin rates from 1000–3600 RPM lasting 4 to 15 minutes respectively. They found that lower spin rates had higher platelet yields, hypothesizing that high rates could cause platelet clumping or disintegration.

Lansdown et al[12] highlighted that patient factors also play a role in platelet concentration. Fasting patients had lower concentrations than those who ate a high-fat meal. The timings of venepuncture can also affect concentration, with the optimal time being in the afternoon. They also surmise from other literature that there appears to be an optimal platelet concentration. If it is too low, i.e. 0.5–1.5x whole blood concentration, there is no enhancement in bone regeneration. If too high, i.e. 6–11x whole blood concentration, then there is a paradoxical inhibitory effect on bone regeneration.

Arora et al[14] reviewed some of the technical aspects in relation to PRP preparation. They stressed the importance of anticoagulants in preventing the coagulation cascade of collected blood. Ethylenediaminetetraacetic acid (EDTA) suppresses platelet degranulation and therefore is not recommended for PRP. Conversely, heparin can cause spontaneous aggregation of platelets in some individuals. Anticoagulant citrate dextrose-A (ACD-A) is the most commonly used in commercial kits. It maintains the optimal pH for platelets at 7.2 while the citrate binds to calcium preventing the coagulation cascade. They also recommend PRP be kept in small diameter tubes with caps (to minimize surface area to atmosphere) as the pH can increase by diffusion of CO_2 out of the plasma, potentially causing spontaneous aggregation.

Etulain et al[15] proposed an optimized protocol for PRP preparation. Their three-pronged approach centred on dilution, 4°C incubation and plasma cryoprecipitate supplementation. The combination of these had an additive effect with greater angiogenesis, greater secretion of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), interleukin-17 (IL-17) and interleukin-8 (IL-8) which translated into faster and more efficient mouse-skin wound repair vs. non-optimized PRP.

Preparation of PRP is vitally important, as it will have a direct impact on the final composition of PRP. Degen et al[16] looked into the compositional differences of five commercially available PRP systems. They found that platelet concentration and capture efficiency was similar amongst all systems, WBC concentration was significantly elevated in all systems compared to whole blood, and variation was seen with pH, RBC and neutrophil levels. The exact implications of differing compositional elements are still unknown and will be considered later in the article. What is clear is the heterogeneity amongst differing commercial PRP systems (Table 1). It is therefore inferable that this heterogeneity limits conclusions drawn from pooled PRP studies containing multiple PRP preparation systems.

At a commercial level, there is a vast array of kits available to prepare PRP with varying concentration of platelet yields and no overall consensus on optimal component concentrations.[17] A systematic review by Chahla et al[18] found that, of 105 studies using PRP in orthopaedics, only 11 provided comprehensive reporting of the preparation protocol that could be used by subsequent investigators. Only 17 studies provided qualitative metrics on the composition of their PRP products. Greater transparency in the reporting of PRP used in clinical and laboratory studies is needed. This must be in conjunction with a unified classification system with international consensus. This must be the direction of future research if the full potential of PRP is to be realized.

Classifications

Over the past decade, PRP use has grown significantly with numerous formulations currently available. Several authors have attempted to classify these preparations in order to give the orthopaedic community the means of comparing formulations, to find the optimal preparations for specific pathologies. The first such classification was proposed in 2009 by Ehrenfest et al[19] (Table 2) who divided preparations by the presence of cell content and fibrin architecture. This qualitative classification gave a starting point but did not take into consideration other subpopulations of cells such as RBCs or neutrophils, which have an important role in the mechanism of action of PRP.

DeLong et al[20] developed on this classification and introduced a quantitative element. The PAW classification (Platelets, Activation, White blood cells) (Table 3) provides a nomenclature based on platelet concentration, activation and WBC count, including the neutrophil subgroup.

Mautner et al,[21] however, argued that the PAW system did not address the effects of the RBC content on PRP preparations and recommended the PLRA classification (Platelet count, Leukocyte content, RBC content, Activation) (Table 4). This system was the first to recommend documentation of the volume of PRP used and the absolute platelet concentration. The authors also suggested the frequency of PRP treatments be recorded if multiple treatments were delivered.

Magalon et al[22] proposed a classification system (Table 5) focused on the quality of the preparation. The DEPA classification (Dose, Efficiency, Purity, Activation) analyses aspects of the production process that were not previously taken into consideration. However, it does not analyse the content of the PRP based on different cell types to the same quantitative level as the PLRA classification.

The latest PRP classification system is MARSPILL (Method, Activation, RBCs, Spin, Platelet concentration, Image guided, Leukocyte concentration, Light activation), developed by Lana et al[23] (Table 6). This is an amalgamation of previous systems, incorporating aspects of the manufacturing process as well as analysing the subgroups of cell types. They believe the focus on peripheral blood mononuclear cells is as important as platelet concentration, and they also incorporate newer concepts such as light activation and the use of image guidance to provide more elements to the classification system.

Numerous authors have developed classification systems for PRP, with each new generation taking into account additional factors that their predecessors had not considered. Due to the rapidly evolving nature of this field and the increased complexity of each preparation, there has not been widespread uptake of a single classification. In turn, none of the aforementioned classifications have been validated at an international consensus level. Barriers to widespread use of these classifications include the problem of oversimplification, such that researchers are wary of the earlier classification systems, which may classify their formulation as equal to other products that have not had favourable outcomes. Alternatively, if the trend of classifications becomes ever more complex, it may pose financial barriers to smaller research groups who may not have the resources to analyse their preparations to the same standard as large-scale pharmaceutical corporations.[13]

Mechanism of action

Platelets are anucleated cytoplasmic fragments of megakaryocytes that differentiate down the myeloid cell lineage.[24] They contain α-granules, often thought of as the storage units of platelets,[25] which studies suggest contain an abundance of growth factors (GFs). These are believed to influence inflammation, angiogenesis, stem cell migration and cell proliferation.[5] Platelets are well known to be the initiators of the healing process; however, not all tissues have a rich blood supply, for example tendons, ligaments and cartilage. This results in relatively low levels of GFs being available to these tissues to enact effective healing. Application of PRP to these, and other, areas can therefore introduce supra-physiological levels of GFs to theoretically stimulate resolution of chronic pathological

Table 1. Component and preparation profile of commercial platelet-rich plasma (PRP) systems

	Arthrex ACP Double Syringe (Arthrex, USA)	Arthrex Angel System (Arthrex, USA)	RegenKit A-PRP (RegenLab, Switzerland)	MyCells (UK)/ Tropocells (UK)/ Cellenis PRP (Estar Medical, Israel)	PRGF / Endoret (BTI, Spain)	Glo PRP (Glofinn, Finland)
PRP type	Plasma-based	Buffy-coat	Variant	Variant	Plasma-based	Variant
Starting volume	15 ml	40–180 ml	8 ml	10 ml	9 ml	9 ml
Platelets	2–3x (~2.5x)	Up to 18x	1.6x	2–5x (4.5x in 2ml)	2x	4–9x
WBCs	Reduction	Adjustable	Reduction	Reduction	Reduction	Increase
RBCs	Adjustable	Adjustable	Reduction	Reduction	Adjustable	No reduction possibility
PRP yield	4–6 ml	2–20 ml depending on composition	4 ml	2–3 ml	2 ml	Adjustable
Closed system	Yes	Yes	No	No	No	No
Needles involved	No	No	Yes	Yes	Yes	Yes
Principle	Centrifugation – closed transfer of PRP	Centrifugation with sensor/valve technology (light absorption) – PRP automatically collected in syringe	Separation gel – open needle transfer of PRP	Separation gel	Manual	Manual
Separation gel	No	No	Yes	Yes	No	No
Anticoagulant	No	Yes	Yes	Yes	Yes	Yes
Centrifugation steps	One	One	One	One	One	Two
Spinning parameters	1500 rpm / 5 min	Depending on program, 3000 rpm or 3500 rpm, 15–30 min	3400 rpm / 5min	1500 g / 10 min	580 / 8 min (+20 min clotting time)	1200 g / 5 min 1200 g / 10 min
Preparation time	10 min	25–40 min	10 min	25 min	30 min	25 min
Handling steps	⩽ 5	5–8	⩽ 5	> 10	5–8	8–10
Centrifuge	Specific	Specific	Specific	Specific	Specific	Specific

	Ortho.pras (Proteal, Spain)	Genesis CS (EmCyte, USA)	PurePRP II (EmCyte, USA)	Y-PRP (Ycellbio Medical, South Korea)	Dr. PRP (SDD Medical Group, UK)
PRP type	Variant	Buffy-coat	Buffy-coat	Buffy-coat	Buffy-coat
Starting volume	20 / 40 ml	30 / 60 ml	60 / 120 ml	15 ml	20 ml
Platelets	2.2x (in 4 ml PRP)	?	8x	7–9x	?
WBCs	Adjustable	Increase	Adjustable	Increase	Adjustable
RBCs	Adjustable	No reduction possibility	Adjustable	Reduction	Adjustable
PRP yield	4–10 ml	3–4 / 7 ml	7 / 14 ml	1–2 ml	5 ml
Closed system	No	Yes	Yes	No	No
Needles involved	No	No	No	Yes	Yes
Principle	Manual	Manual	Manual, PRP transferred to a separate container after first centrifugation	Manual	Manual, after first centrifugation plasma and RBC container are separated
Separation gel	No	No	No	No	No
Anticoagulant	Yes	Yes	Yes	Yes	Yes
Centrifugation steps	One	One	Two	One	Two
Spinning parameters	1800 rpm / 8 min	4400 rpm / 5 min	3800 rpm / 1.5 min; 3800 rpm / 5 min	3200–3600 rpm / 4 min	3400 rpm / 4 min; 3500 rpm / 2 min
Preparation time	20 min	15 min	20 min	20 min	20 min
Handling steps	8–10	5–8	5–8	5–8	> 10
Centrifuge	Specific	Specific	Specific	Specific	Specific

	SW-PRP (Seawon meditech, South Korea)	Biomet GPS (Zimmer Biomet, USA)	Harvest SmartPReP (Terumo, USA)	CPunT (Eltek Group, Italy)	Magellan (Arteriocyte Medical Systems, USA)
PRP type	Buffy-coat	Buffy-coat	Buffy-coat	Buffy-coat	Buffy-coat
Starting volume	25 ml	30 / 60 ml	20 / 60 ml	50 ml	30–160 ml
Platelets	?	9.3x	4.3–6.6x	4–5x	?
WBCs	Increase	Increase	Increase	Adjustable	Adjustable
RBCs	No reduction possibility	No reduction possibility	No reduction possibility	Adjustable	Adjustable
PRP yield	2 ml	3 / 6 ml	3 / 7 / 10 ml	10 ml	3–10 ml
Closed system	No	No	No	Yes	Yes
Needles involved	No	No	Yes	Yes	No
Principle	Manual, after first centrifugation plasma and RBC container are separated	Dual buoy system – extraction of PRP through separate luer port	Two chamber bucket + floating shelf – open needle transfer of PPP and PRP	Centrifugation – first separation automated in electromechanical device, second separation manual	Centrifugation with sensor/valve technology (light absorption) – PRP automatically collected in syringe
Separation gel	No	No	No	No	No
Anticoagulant	Yes	Yes	Yes	Yes	Yes
Centrifugation steps	Two	One	One	Two	One
Spinning parameters	3850 rpm / 7 min; 3850 rpm / 8 min	3200 rpm / 15 min	1000 g / 14 min	1200 rpm / 10 min; 1900 rpm / 10 min	Depending on programme, 12–17 min
Preparation time	40 min	30 min	20 min	30 min	25–30 min
Handling steps	> 10	5–8	8–10	> 10	5–8
Centrifuge	Specific	Specific	Specific	Specific	Specific

Note. ACP, autologous conditioned plasma; PRGF, plasma rich in growth factors; BTI, biotechnology institute; WBC, white blood cell; RBC, red blood cell. GPS, gravitational platelet system.

Table 2. Ehrenfest classification

Pure platelet-rich plasma (P-PRP)	Leukocyte-poor, low-density fibrin network
Leukocyte and platelet-rich plasma (L-PRP)	Contains leukocytes and low-density fibrin network
Pure platelet-rich fibrin (P-PRF)	Without leukocytes and high-density fibrin network
Leukocyte and platelet-rich fibrin (L-PRF)	Contains leukocytes and high-density fibrin network

Table 3. PAW (Platelets, Activation, White blood cells) classification

Platelets	Concentration (/μL)	⩽ baseline	P1
		> baseline – 750,000	P2
		> 750,000 – 1,250,000	P3
		> 1,250,000	P4
Activation	Exogenous		X
White blood cells (WBCs)	Total WBCs	Above baseline	A
		⩽ baseline	B
	Neutrophils	Above baseline	α
		⩽ baseline	β

Table 4. PLRA (Platelet count, Leukocyte content, RBC content, Activation) classification

	Criteria	Final Score
P Platelet count	____P	_____M
	Volume Injected	Cells/μL
L Leucocyte content*	> 1%	+
	< 1%	–
R Red blood cell content	> 1%	+
	< 1%	–
A Activation**	Yes	+
	No	–

*If white blood cells are present (+), percentage of neutrophils should be reported.
**The method of exogenous activation should be reported.

processes. Commercial ELISA (Vector Laboratories, Burlingame, CA; Quantikine Immunoassay, R&D Systems, Minneapolis, Minnesota) and Luminex kits (Luminex Corporation, Austin, Texas) were used to accurately quantify GFs in software based statistical analysis in the following section.

Once recruited to an area of injury, platelet adhesion is facilitated through adhesive glycoproteins secreted by α-granules,[26] including vitronectin, fibronectin, thrombospondin and von Willebrand factor.[27,28] Once the clot is formed the platelets are activated,[29] allowing the release of the GFs from α-granules to stimulate healing.

There are myriad GFs contained within α-granules, of which the complex interchange amongst them is hypothesized to be of additional benefit to the healing process beyond simply introducing a higher concentration of platelets at hypovascular sites.[24]

Growth factors enact their functions primarily via ligand binding to associated extracellular cell surface receptors, which signal intracellular cytoplasmic proteins to attach to phosphorylated tyrosine. This is followed by multiple phosphorylation and activation steps of protein kinases within the cytoplasm, finally leading to translocation of a phosphorylated kinase to the cell nucleus. This phosphorylates transcription factors enabling gene transcription and ultimately the execution of the encoded function.[30,31]

Growth factors contained within α-granules thought to be crucial to the efficacy of PRP include platelet-derived growth factor (PDGF), VEGF, the transforming growth factor-β superfamily (TGF-β), fibroblast growth factor (FGF) and insulin-like growth factor (IGF). PDGF is able to initiate callus formation via chemotaxis and mitogenesis of fibroblasts and chondrocytes,[32,33] along with chemotaxis of mesenchymal stem cells (MSCs).[34] The promotion of endothelial cell proliferation by PDGF also has an important role in angiogenesis.[35] VEGF is involved in neovascularization through its strong endothelial chemokine and mitogenic properties.[36] TGF-β is well established as a promoter of chondrogenesis,[37] but has also been shown to: stimulate osteogenic MSC differentiation[38] and undifferentiated mesenchymal cell proliferation; regulate the mitogenic effects of other GFs; and inhibit macrophage and lymphocyte proliferation.[39] The FGF family is involved in multiple biological processes including osteoblastogenesis,[38,40] growth and differentiation of chondrocytes and MSCs.[39] IGF regulates the proliferation and maturation of chondrocytes[41,42] and IGF-1 may down-regulate expression of programmed cell death 5 (PDCD5), thereby inhibiting apoptosis of osteoarthritic chondrocytes.[43]

In addition to GF release following platelet activation, Xie et al[44] demonstrated that PRP also forms a fibrin gel, which acts as a conductive bioscaffold to allow incorporation of migrating cells for tendon healing. Entrapment of GFs within a fibrin matrix[45,46] may hold the key to controlled release of GFs at the intended site of action. However, it is important to note that cellular response to GFs is limited by number of target receptors available on cell surfaces, therefore high platelet concentrations and subsequent GF release may not be of benefit.[26] This may explain why PRP preparations with GFs over six times the physiological concentration may have an inhibitory effect.[47]

This leads on to an important point, that while there are many GFs that have been shown to have beneficial effects on cartilage, tendons, bone and other tissues, there are other components that can have negative effects such as pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and interleukin-1β (IL-1β).[48] For example, Browning et al[49] demonstrated an increase in MMP-1 and MMP-3 in osteoarthritis (OA) synoviocytes incubated with PRP. Thereby suggesting PRP application to joints may lead to accelerated cartilage breakdown due to a pro-inflammatory response. Most in vitro studies support PRP

Table 5. DEPA (Dose, Efficiency, Purity, Activation) classification

	Subgroup	Description
Dose of injected platelets	Very high	> 5 Billion injected platelets
	High	3–5 Billion
	Medium	1–3 Billion
	Low	< 1 Billion
Efficiency of production	High	Recovery rate in platelets > 90%
	Medium	70–90%
	Low	30–70%
	Poor	< 30%
Purity of PRP	Very pure	Platelets in PRP > 90%
	Pure	70–90%
	Heterogeneous	30–70%
	Whole-blood	< 30%
Activation process	Autologous thrombin Calcium chloride	

Table 6. MARSPILL classification

M	Method	Handmade	H
		Machine	M
A	Activation	Activated	A+
		Non-activated	A–
R	Red blood cells	Rich	RBC-R
		Poor	RBC-P
S	Spin	One spin	Sp1
		Two spins	Sp2
P	Platelet concentration		PL 2–3
			PL 4–6
			PL 6–8
			PL 8–10
I	Image guided	Guided	G+
		Not-guided	G–
L	Leukocyte concentration	Rich	Lc-R
		Poor	Lc-P
L	Light activation	Activated	A+
		Not-activated	A–

use in cartilage tissue because of the ability to increase chondrocyte proliferation and production of matrix molecules whilst not affecting chondrogenic phenotype.[50] However, the importance of platelet-derived GF dosage has also been highlighted through the different results they can produce.[51]

Perhaps the biggest area of controversy surrounding PRP is the concentration of cellular components, particularly leucocytes. There has been debate around whether leucocytes are adverse because of cytokines causing inflammation and subsequent weaker fibrotic tissue and/or proteases and reactive oxygen species they release,[50] or beneficial as a result of cytokines that can prevent infection and improve healing.[16] This is something we will explore in the following section.

Applications

The ubiquitous nature of the mechanism of action of PRP suggests that, in theory, it can be applied to multiple pathologies to aid the body's natural healing processes. We will look at these pathologies in detail and the type of PRP used (see Table 7). Unless stated, all the evidence included in this section is either level 1 (systematic review of randomized controlled trials [RCTs] or individual RCT) or level 2 (systematic review of cohort studies and RCTs). The Coleman Modified Scores given are the average of the papers analysed.

Tendinopathies

The majority of research into PRP treatment for tendinopathy centres on lateral epicondylitis, where PRP has been shown through systematic review[52] to have a better, albeit delayed, therapeutic effect compared to corticosteroid injection for up to two years post injection (CMS 53). Three of the five RCTs analysed used leukocyte-rich PRP (L-PRP), the others did not document the type of PRP used. On further analysis, the RCTs that showed the most significant improvements compared to corticosteroid, were those documenting L-PRP was used.

Systematic review and meta-analyses of studies assessing PRP efficacy in Achilles tendinopathy[53] showed that PRP conferred no clinical benefit when compared to saline placebo or an eccentric loading programme (CMS 65). Two of the studies used L-PRP, the other did not document the type of PRP used.

A systematic review and meta-analysis of two RCTs assessing L-PRP efficacy for patellar tendinosis[54] suggested that PRP was statistically better than dry needling or extracorporeal shockwave therapy at six months post treatment (CMS 66).

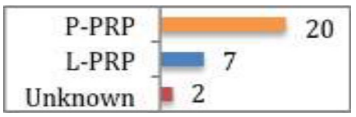
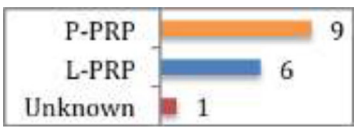
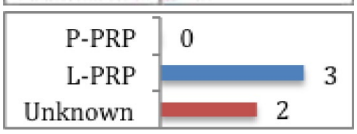
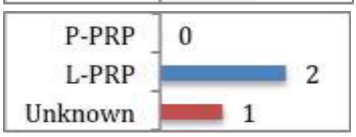
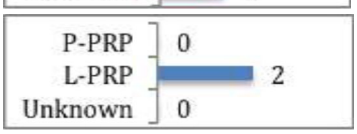
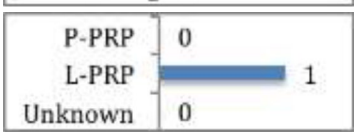
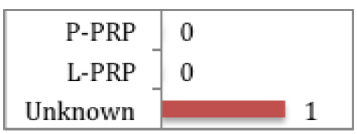
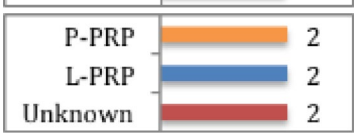
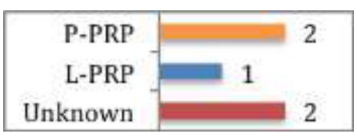
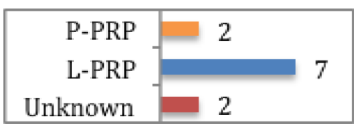
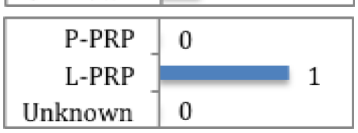
There have been two RCTs assessing PRP versus saline injection[55] and dry needling[56] respectively in the treatment of rotator cuff disease (tendinopathy or partial tears). Rha et al[56] found that PRP provided more symptomatic relief and functional improvement (based on greater reduction in shoulder pain and disability index) at six weeks to six months post injection than dry needling (CMS 66). The type of PRP was not documented. Whereas, Kesikburun et al[55] found no difference between L-PRP and saline injections at any follow-up point up to a year post injection (CMS 71).

The combined evidence for PRP efficacy in tendinopathies shows that in the studies where PRP has shown statistical improvement to control measures, it is L-PRP that has been used.

Cartilage pathology

Laver et al[57] reviewed all studies that assessed PRP for the treatment of degenerative cartilage pathology. A total of 29 studies were included, nine prospective RCTs, four prospective comparative studies, 14 case series, and two retrospective comparative studies. Of the nine RCTs, all reported improved symptoms with PRP groups at the final 12-month follow up, seven of which were significantly

Table 7. Summarized platelet-rich plasma (PRP) evidence by indication and PRP type

Indication	Findings	PRP type studied
Osteoarthritis	**Laver et al** Improved symptoms with PRP at 12-month follow up. Significantly improved in 7 of the 9 RCTs included. Trend towards improved outcomes in younger patients/early OA changes with PRP.	
	Chang et al Improved functional outcomes with PRP up to a year post treatment. Less severe OA showed more benefit from PRP.	
Lateral epicondylitis	**Ben-Nafa and Munro** Improved outcomes for up to 2 years post treatment with PRP compared to corticosteroid injection.	
Achilles tendinopathy	**Gholami et al** No clinical benefit shown between PRP and saline placebo injection or eccentric loading programme.	
Patella tendinosis	**Dupley and Charalambous** Statistically significant improvement in functional scores at 6 months post treatment with PRP compared to dry needling or extracorporeal shockwave therapy (ESWT).	
Rotator cuff disease	**Kesikburun et al** No difference demonstrated between PRP and saline at any follow up point (followed up for 1 year) for rotator cuff tendinopathy or partial tears.	
	Rha et al Significant functional improvement and greater symptomatic relief at 6 weeks to 6 months post treatment with PRP compared to dry needling for partial tears.	
Acute muscle injury	**Grassi et al** Meta-analysis demonstrated statistically significant reduction in return to sport time (7.17 days) with PRP compared to controls (none/haematoma evacuation/saline injection/platelet-poor plasma (PPP) injection). Subgroup analysis of only double-blinded RCTs (both using P-PRP) showed no difference between PRP and controls (haematoma evacuation/saline injection). Subgroup analysis of hamstring injuries (2 using L-PRP, 1 using P-PRP) showed no difference between PRP and controls (none/saline injection/PPP injection).	
Surgical augmentation: rotator cuff repair	**Cohn et al** Of the 5 studies included, 1 showed less pain in the early post-operative period and increased strength of external rotation at 3 months post op with L-PRP + surgery. Another study showed a 20% reduction in re-rupture rate and significant improvement in shoulder function post op in PRP + surgery (PRP type unknown). The other 3 studies showed no significant differences with the addition of PRP.	
Surgical augmentation: ACL reconstruction	**Figueroa et al** Of the 9 RCTs included, 2 studies showed PRP might reduce graft maturity time (one used L-PRP, the other type was unknown).	
Sacroiliac joint instability	**Ko et al** Clinically and statistically significant improvement in pain at 12 months post treatment with L-PRP. Clinically significant improvement still present at 4 years post treatment.	

Note. P-PRP, pure platelet-rich plasma; L-PRP, leukocyte-rich platelet-rich plasma; RCT, randomized controlled trial; ACL, anterior cruciate ligament.

superior results. Generally, all studies appear to show overall positive results and clinical benefit from PRP, irrespective of methodological variation. Interestingly, there was a trend towards improved outcomes in either patients of younger age or early OA changes. Only one study followed up patients beyond 12 months (to two years). In this study, while there was symptomatic improvement at 12 months follow up; there was significant decrease in

functional scores at two years, albeit still higher than the baseline level (CMS 61). Twenty studies used pure PRP (P-PRP), seven studies used L-PRP and two studies did not document PRP leukocyte content. Of the nine RCTs reporting improved outcomes, eight used P-PRP, while one used L-PRP. Whilst not directly investigated, these findings suggest P-PRP is more suitable to intra-articular pathology.

Further review and meta-analysis by Chang et al[58] reinforced the findings of Laver et al.[57] Specifically that less severe OA benefits more from PRP, and PRP is likely to be superior to hyaluronic acid for functional outcomes and have longer duration of action (up to a year).

A case series by Ko et al[59] (level 4) has even shown L-PRP can significantly reduce chronic low back pain in patients with sacroiliac joint (SIJ) instability when injected under ultrasound guidance into the SIJ, lasting up to four years (CMS 59).

Acute muscle injuries

A systematic review and meta-analysis of six RCTs assessing the effectiveness of PRP in reducing return to sport times, demonstrated that when taking into account all six studies, the return to sport time was significantly shorter (by 7.17 days) in the PRP group (CMS 67).[60] However, when only the double-blinded studies or studies including only hamstring injury were included in the analysis, no significant difference was noted. In addition, re-injury rates were similar between PRP and controls across studies. There were no significant differences regarding pain, muscle strength, flexibility, muscle function or healing (on ultrasound scan or magnetic resonance imaging).[60] Two studies used P-PRP, two used L-PRP, and two did not document PRP type. These findings suggest that when return to play as early as possible is the primary motivation (such as for professional sport) it can be worth using PRP. However, the results are varied and the type of PRP best suited is unknown.

Surgical augmentation

Multiple studies have looked at the use of PRP as an augmentation for surgery to expedite healing and recovery time. The majority of studies assessing this are focussed on rotator cuff repair and anterior cruciate ligament (ACL) surgery. Cohn et al[61] reviewed five RCTs assessing the effect of PRP versus no treatment in conjunction with rotator cuff repair. Only two of the studies showed any benefit. Randelli et al[62] demonstrated less pain in the early post-operative period and increased strength of external rotation at three months post-operatively in the L-PRP group (CMS 76). Interestingly, subgroup analysis of grade 1 and 2 tears showed greater strength of external rotation from 3 to 24 months post-operatively, suggesting milder tears may benefit more from L-PRP. Jo et al[63] looked at PRP efficacy in large rotator cuff tears and found that re-rupture was 20% lower in the PRP + surgery group compared with surgery alone, as well as the overall shoulder function being significantly better (CMS 73). However, the type of PRP used was not described. The other RCTs showed no significant differences in peri-operative morbidity, clinical outcomes of structural integrity between PRP + surgery and surgery alone. Two of the studies used P-PRP while the other did not specify the PRP classification. Overall, these results show L-PRP may be of benefit in rotator cuff repair. A 20% reduction in large tear re-rupture is certainly worth the addition of PRP. However, the type was not documented. Interestingly, of the three RCTs showing no benefit with these tendon injuries, two used P-PRP and the other was unspecified.

A systematic review of nine RCTs and two cohort studies assessing PRP use in ACL surgery[64] (level 3) showed there is evidence that adding PRP to the graft or tunnels could be beneficial in expediting graft maturity (CMS 60). Seven studies used L-PRP, two used P-PRP and two did not document PRP type. Similarly to muscle injuries, where early return to play is a crucial, these finding suggest the addition of PRP during ACL reconstruction may be of benefit. However, the type of PRP is again unclear.

Discussion

The breadth of applications for PRP in orthopaedics is vast. There have been encouraging results in a multitude of studies focussing on different potential indications. However, the sheer scale of heterogeneity across studies makes it difficult to draw clear conclusions from promising results. In addition, many studies will group soft tissue injuries together in their analysis, thereby further compounding the heterogeneity and potentially obscuring the true impact that PRP may have on specific soft tissue pathologies.

Too often the classification of PRP is not made clear, making it difficult to establish trends of PRP efficacy for differing pathologies. This is especially important when many clinicians are matching the type of PRP to specific pathologies, based on loose clinical indications from studies where the primary aim was not the comparison of PRP types for specific pathologies. Throughout the applications section we have highlighted the PRP type used in each study and, in conjunction with the results, thereby suggested which PRP type appears more effective for each indication based on the analysed evidence. However, it must be emphasized that no specific trends of impaired or improved outcomes of one PRP type over another have been observed for any indication. This is due to the methodologies of the analysed studies not being specifically designed to answer the question 'Which PRP type is best for this indication?' Therefore, as there is no direct comparison between these two PRP formulations for any

indication, definitive conclusions cannot be made. This highlights the importance for future research to compare PRP formulation efficacy across applications, or at least state clearly what PRP formulation is being used so it can be accurately classified.

While there has been no direct comparison of PRP types for different applications within the literature, L-PRP appears to be more effective in chronic tendinopathies. This is due to the natural first stage of tendon healing including inflammation from leucocytes and catabolic cytokines.[66] In contrast, P-PRP seems to be more beneficial in cartilage pathology.[65,67] This may be because L-PRP has been shown to cause a significantly greater acute inflammatory response and increased synoviocyte cell death.[67,68]

Conclusion

Going forward, there needs to be standardization of certain parameters regarding PRP research. Murray et al[69] have produced a comprehensive 23-statement checklist that all future clinical studies in PRP should adhere to, with the aim of streamlining PRP research towards yielding robust evidence.

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ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest relevant to this work.

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