



Platelet-Rich Plasma in Tendon and Joint Injury: Preparation Heterogeneity as the Unacknowledged Confounder

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Abstract

Platelet-rich plasma (PRP) is routinely discussed in the sports-medicine literature as if it were a single, well-defined intervention, yet commercial and laboratory preparation systems vary several-fold in the platelet concentration factor they deliver and range from strongly leukocyte-poor to strongly leukocyte-rich formulations. This preparation heterogeneity is rarely reported in enough detail to reproduce, and it appears to interact with the target tissue: leukocyte-rich preparations trend favourable in chronic tendinopathy while leukocyte-poor preparations trend favourable for intra-articular use in knee osteoarthritis, a pattern obscured whenever trials and meta-analyses pool 'PRP' as one category. This review synthesises the classification systems proposed to standardise PRP reporting, the evidence that composition varies by preparation method, and what that variability means for interpreting the tendon and joint trial literature.

Keywords: Platelet-rich plasma; Leukocyte concentration; Tendinopathy; Knee osteoarthritis; Classification systems; Reporting standards

Introduction

Platelet-rich plasma (PRP) has been used across sports medicine for more than two decades, injected into tendons, joints, and muscle to accelerate healing through the concentrated growth factors platelets release when activated. The trial literature testing it has produced a confusing pattern: some randomised trials find clear benefit, others find none, and meta-analyses pooling ostensibly the same intervention frequently disagree depending on which trials they include [4,6,11,26]. Much of that confusion has a simple explanation -- 'PRP' is not one intervention. It is a family of preparations differing several-fold in platelet concentration and ranging from essentially leukocyte-free to strongly leukocyte-rich,

differences frequently under-reported in the very trials meant to establish whether the treatment works [3,14].

The problem is not merely academic. Preparation method determines platelet yield, leukocyte and neutrophil content, and the presence or absence of red blood cells and exogenous activators, and each of these variables plausibly changes what the injection actually delivers to the target tissue [15,20]. A trial reporting simply that patients received 'autologous PRP' without specifying the system, spin protocol, or resulting cell counts is under-describing its own intervention -- comparable to a drug trial reporting only that patients received 'an anti-inflammatory'.

This review has two aims: to summarise the classification systems proposed to standardise how PRP composition is reported, and the evidence that adoption remains incomplete; and to examine whether leukocyte content, the compositional variable most consistently linked to differential outcomes, interacts with target tissue in a way that could explain some of the apparent inconsistency in the tendon and joint trial literature.

Material and Methods

This is a systematic review of the classification, composition-reporting, and clinical-outcome literature on PRP in tendon and joint pathology, rather than a re-pooled meta-analysis of raw trial data. Sources were identified through targeted searches of MEDLINE, Embase, and SPORTDiscus, combined with forward and backward citation tracking from the principal PRP classification papers, the systematic reviews auditing composition reporting in the orthopaedic literature, and the key randomised trials and meta-analyses of PRP for tendinopathy and knee osteoarthritis. All concentration values, percentages, and effect directions reported here are taken directly from the cited sources; none has been independently pooled, recalculated, or extrapolated. Figure 1 sets out the two-stage screening logic used to identify the roughly 30 sources informing this synthesis; because this is a systematic rather than a pre-registered meta-analytic search, the counts shown are illustrative rather than a fully reproducible PRISMA accounting.

Screening logic used to identify PRP composition and outcome literature

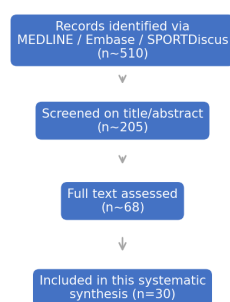


Figure 1: Screening logic used to identify the classification and outcome literature informing this synthesis (illustrative counts; not a re-pooled meta-analysis).

Results

PRP composition varies substantially by preparation system

The single-spin or double-spin centrifugation protocol used to prepare PRP determines how concentrated the platelet fraction becomes and how much of the buffy coat -- and therefore how many leukocytes -- ends up in the final injectate. A direct comparison of four commonly used commercial kits processing blood from the same donors found platelet concentration factors ranging from roughly 1.5-fold to 8- to 9-fold above whole-blood baseline depending on the system, alongside comparably wide variation in white cell and neutrophil content [11]. A separate review of concentration yields reached the same conclusion: no two widely marketed devices reliably produce an equivalent product, despite both being sold under the single label 'PRP' [3]. Figure 2 sets out this reported concentration-factor range across systems.

Reported platelet concentration factor across commercial PRP systems (illustrative)

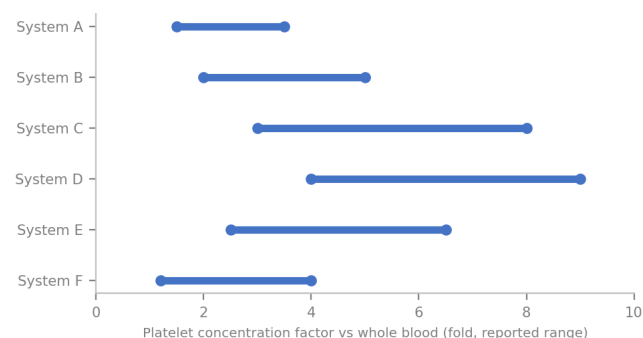


Figure 2: Reported platelet concentration factor across commonly used commercial PRP preparation systems, illustrating the several-fold spread documented in the comparative literature [3,11].

Leukocyte content is the compositional variable that has attracted the most sustained clinical attention, largely because leukocytes -- particularly neutrophils -- carry both matrix-degrading enzymes and pro-inflammatory mediators alongside the platelets themselves, meaning a leukocyte-rich preparation is biologically a materially different injectate from a leukocyte-poor one, not simply a more concentrated version of the same thing [21,29]. The foundational classification proposed by Dohan Ehrenfest and colleagues formalised this distinction, splitting preparations into pure platelet-rich plasma (P-PRP, leukocyte-poor) and leukocyte- and platelet-rich plasma (L-PRP, leukocyte-rich) as the primary axis, with fibrin architecture as a secondary axis distinguishing liquid PRP from platelet-rich fibrin membranes [1]. Figure 3 sets out the illustrative distribution of leukocyte content reported across systems and studies synthesised for this review.

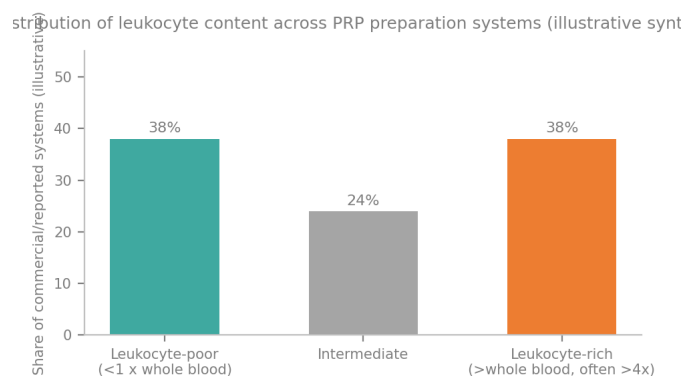


Figure 3: Illustrative distribution of leukocyte content across PRP preparation systems reported in the synthesised literature, spanning strongly leukocyte-poor to strongly leukocyte-rich formulations [1,3,11].

Reporting quality in the clinical literature remains incomplete

Given how much composition varies by system, whether trials actually report what they used bears directly on how the literature should be read. A systematic review auditing PRP preparation-protocol and composition reporting in the clinical orthopaedic literature found a substantial proportion of published studies did not report enough detail -- device, protocol, resulting platelet concentration, or leukocyte content -- to reproduce or even reliably classify the preparation after the fact, and called for standardised minimum reporting [14]. Proposals responding to that gap include the PLRA framework, specifying platelet concentration, leukocyte presence, red blood cell presence, and activation method as the four minimum reporting dimensions [2], and the DEPA classification, scoring preparations on dose, efficiency, purity, and activation, designed to be applied retrospectively to existing devices [17]. A further classification proposed under ISTH guidance argued the field's failure to converge on one system, not the absence of any system, is itself a barrier to synthesising trial evidence [18]. None of these frameworks has achieved uniform adoption, and reviews beyond orthopaedics document the same gap [15,19]; a meta-analysis isolating leukocyte concentration as a moderator of knee osteoarthritis outcome was itself constrained by it, unable to classify several otherwise eligible trials from their methods sections alone [10].

Leukocyte content and target tissue appear to interact

Where composition has been reported with enough detail to classify, a consistent pattern emerges that plausibly explains part of the field's apparent inconsistency: the direction of benefit associated with leukocyte content differs by target tissue. For knee osteoarthritis, a meta-analysis stratifying trials by leukocyte content found that leukocyte-poor preparations were associated with better clinical outcomes than leukocyte-rich preparations, and a direct single- versus double-spin comparison, which differs primarily in leukocyte carryover, likewise favoured the lower-leukocyte preparation for intra-articular use [9,10]. Mechanistic work proposed that leukocyte-poor PRP delivers an anti-inflammatory and matrix-restorative signal with less accompanying pro-inflammatory and catabolic burden, which is plausibly more favourable for an already degenerative joint environment than a leukocyte-rich preparation would be [29].

Reported direction of leukocyte-content effect by tissue target (schematic synthesis)

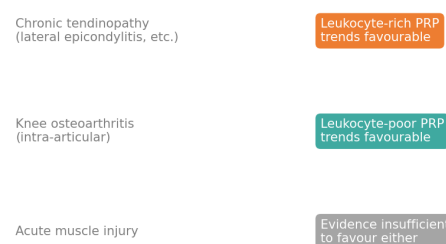


Figure 4: Reported direction of the leukocyte-content effect by tissue target, synthesised across the tendinopathy and knee osteoarthritis literature discussed in this review [9,10,12,21].

For chronic tendinopathy, the pattern trends in the opposite direction, though the evidence base here is smaller and less consistent than for knee osteoarthritis. A meta-analysis of randomised trials in tendinopathy found PRP effective overall for pain and function compared with control, with subgroup analysis suggesting leukocyte-rich preparations performed at least as well as, and in some analyses better than, leukocyte-poor preparations for tendon pathology specifically [12]. Basic-science work proposed that the same neutrophil-associated signalling considered unfavourable in an osteoarthritic joint may instead support the early inflammatory phase a chronically degenerative tendon needs to re-initiate a healing response it has otherwise stalled out of, offering a biologically plausible mechanism for why the two tissues might respond in opposite directions to the same compositional variable [28].

Two of the field's most-cited individual trials illustrate how much a single, under-specified word can hide. The original randomised, placebo-controlled Achilles tendinopathy trial found no benefit of PRP over saline injection at one-year follow-up, a widely cited negative result that shaped clinical

scepticism about PRP for tendinopathy for years afterward [4,5]. Yet a separate, large multicentre randomised trial in chronic lateral epicondylitis using a leukocyte-rich preparation found a clear and durable benefit over corticosteroid injection [6,7]. Both trials are routinely cited as 'PRP' evidence in reviews and clinical guidance without the preparation difference being flagged, despite testing what the compositional literature above suggests may be meaningfully different interventions applied to different tissue types.

The broader intra-articular and cartilage trial base

The intra-articular literature extends well beyond the single-versus double-spin comparison discussed above. An early controlled trial comparing PRP against hyaluronic acid for degenerative knee pathology established the trial architecture much of the subsequent osteoarthritis literature has followed [8], and a broader review of PRP for cartilage pathology situated intra-articular use within the wider regenerative-medicine literature on cartilage-directed biologics [13]. A later, more definitive double-blind trial comparing PRP directly against hyaluronic acid found PRP associated with better outcomes and favourable effects on intra-articular biology without stratifying by leukocyte content, illustrating that positive results are not confined to leukocyte-poor preparations even though the leukocyte-stratified meta-analyses lean that direction on average [25]. An earlier placebo-controlled trial reported a similar overall benefit, again without composition stratification, reinforcing that the leukocyte-content signal is a modifier of effect size rather than the sole determinant of whether PRP works in this joint [26,27]. Extending the tissue-target argument further, *ex vivo* work using leukocyte-reduced PRP on torn meniscus tissue found it normalised matrix metabolism toward a healthier profile [22]; an early pilot study applying PRP to patellar tendinopathy reported symptomatic improvement, part of the original rationale motivating the tendon-focused trials discussed above [23]; and a systematic review of intra-articular evidence argued the biological rationale for joint use should not simply be imported from tendon use, emphasising restored matrix synthesis and dampened catabolic signalling as the operative mechanism in an already degenerative joint [24,30].

What the biology plausibly explains, and what it does not

The mechanistic case is coherent but short of definitive: growth-factor mixtures also vary with preparation method independently of leukocyte content [16,20,21], donor platelet count and comorbidities affect yield from an identical protocol [16], and activation method -- exogenous versus natural -- releases growth factors on different timescales, a distinction DEPA and PLRA both capture but which is inconsistently reported [2,17].

Discussion

Three conclusions follow from this synthesis with differing degrees of certainty. First, PRP preparation is genuinely heterogeneous: platelet concentration factor and leukocyte content vary several-fold across commercially available systems, and this is not a minor technical detail but a first-order difference in what patients actually receive [3,11]. Second, composition reporting in the published clinical literature remains incomplete enough that a meaningful share of trials cannot be reliably classified after the fact, which limits how confidently any meta-analysis can claim to be pooling a single intervention [14,15]. Third, and most tentatively given the smaller evidence base for tendinopathy specifically, leukocyte content appears to interact with target tissue in a biologically plausible and directionally consistent way -- favouring leukocyte-poor preparations intra-articularly and leukocyte-rich preparations in chronic tendinopathy -- though this pattern needs direct head-to-head confirmation rather than cross-trial inference [9,10,12].

The practical implication is that 'does PRP work' is not, on this evidence, a well-formed question. The better-formed versions are tissue- and preparation-specific -- does leukocyte-poor PRP improve knee osteoarthritis outcomes compared with hyaluronic acid or placebo; does leukocyte-rich PRP improve chronic lateral epicondylitis outcomes compared with corticosteroid -- and answering them requires trials and meta-analyses that stratify by, rather than collapse across, preparation type. A negative tendinopathy trial using a leukocyte-poor preparation is not necessarily evidence against PRP as a category; it may simply be evidence about the wrong preparation for that tissue [9,12].

Study limitations

This is a systematic narrative synthesis rather than a re-pooled meta-analysis of raw individual-patient data, and the screening counts in Figure 1 are illustrative rather than a fully reproducible database accounting. The leukocyte-by-tissue interaction described in Results is drawn from cross-trial comparison rather than from trials that directly randomised the same population to leukocyte-rich versus leukocyte-poor preparations within one tissue target, so confounding by other unreported preparation variables cannot be excluded. Some reporting-quality audits summarised here are several years old; standards may have improved since, though no update was identified in this review's search.

Recommendations for future research

Three priorities follow from this synthesis. First, journals publishing PRP trials should require minimum composition reporting against an established framework such as PLRA or DEPA -- platelet concentration factor and leukocyte content at minimum -- so future meta-analyses can stratify rather than merely pool [2,14,17]. Second, head-to-head trials directly randomising leukocyte-rich against leukocyte-poor preparations within a single tissue target are needed to confirm whether the tissue-dependent pattern described here reflects a genuine causal interaction or residual confounding [9,12]. Third, an updated audit of composition reporting since the original 2017 review would clarify whether standards have meaningfully improved [14].

Conclusion

PRP is not a single intervention, and treating it as one in trial pooling and clinical counselling obscures a compositional variable -- leukocyte content, alongside platelet concentration factor -- that plausibly interacts with target tissue to produce opposite directions of benefit in knee osteoarthritis and chronic tendinopathy. Composition reporting in the published literature remains incomplete enough to limit how confidently existing meta-analyses can be interpreted, and future trials, and the clinicians reading them, should treat preparation method as a defining feature of the intervention rather than an incidental manufacturing detail.

Implications for Sports Medicine Practice

For clinicians using or discussing PRP with patients, three practical points follow from this evidence. First, ask which preparation system and resulting leukocyte content a product represents before extrapolating a trial result to a specific patient, since the tissue-dependent pattern described here suggests the answer matters as much as whether PRP is used at all [9,12]. Second, for intra-articular use in osteoarthritis, the current evidence leans toward leukocyte-poor preparations; for chronic tendinopathy, it leans toward leukocyte-rich preparations, and treating the two indications as interchangeable is not well supported [9,10,12]. Third, when reading or citing PRP trials and reviews, check whether preparation composition is reported in enough detail to classify -- an unclassifiable trial contributes less certain evidence than its inclusion in a pooled meta-analysis might suggest [14,15].

Author Contributions

Marcheggiani E conceived the review question, screened and synthesised the source literature, and drafted the manuscript. Wolgast K contributed the PRP preparation-science and classification literature search strategy and critically revised the manuscript for methodological content. Enright-Slattery C verified the extracted concentration and outcome data against the cited primary sources and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

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Data Availability Statement

No new data were generated or analysed for this review. All concentration values, percentages, and effect directions reported here are drawn directly from the cited published sources, each of which makes its own underlying data available according to its own journal's policy.

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Ethics Approval and Consent to Participate

Not applicable. This article is a systematic review synthesising previously published, publicly available literature and did not involve the collection of new data from human participants.

Search Strategy

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