

Platelet-rich plasma

RENEWED SCIENTIFIC UNDERSTANDING MUST GUIDE APPROPRIATE USE

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Growth factors released by platelets are recognised to perform a wide range of regenerative functions including the proliferation and recruitment of stem cells, modulation of local inflammatory responses and stimulation of new blood vessel formation.¹ As such, there is a good rationale for using platelet-rich concentrates to accelerate healing in musculoskeletal conditions where such processes would be desirable. Promising preliminary initial *in vitro* studies,^{2,3} modest regulatory barriers, and public appetite for new treatments have all spurred a rush to find applications in which platelet-rich plasma (PRP) may incur clinical benefit.²⁻⁴ Popularity has been further fuelled by testimonials from celebrity athletes including Tiger Woods⁵ and Rafael Nadal.⁶ PRP is now increasingly being used in the management of musculoskeletal injuries, despite a lack of robust clinical evidence supporting its efficacy. In the race to clinical translation, hundreds of clinical trials were launched without full characterisation of PRP attributes and optimisation of preparations.⁷ There are over 400 clinical trials currently ongoing evaluating the use of PRP in a range of clinical applications.⁸ Unfortunately, this rush to treat patients has occurred at the expense of the basic scientific understanding of the underlying pathophysiology of each condition, and of the composition of PRP preparations. Clinical trials are being launched without full knowledge of what PRP contains, what 'doses' and methods of delivery are most effective, and without comprehensive scientific understanding of the mechanisms by which it may benefit the patient. These studies have so far yielded disappointing results.^{9,10} While PRP may ultimately be considered the 'fad du jour', there is also a danger that potentially beneficial treatments are dismissed as non-effective simply because suboptimised preparations were used in these studies. We will only truly know if PRP

can be of therapeutic benefit if the scientific/clinical community accepts that shortcuts cannot be taken, and adopts a comprehensive 'back to basics' approach to developing therapies.

What is PRP?

The heterogeneous nature of PRP preparations is often not appreciated by clinicians and patients. PRP is a term used to describe concentrates of platelets prepared from autologous blood. This represents a broad spectrum of preparations containing variable levels of platelets, leucocytes and red cells with over 300 distinct cytokines and growth factors reported to date.^{11,12} In order to encourage release of these growth factors, platelets can be activated using several different methods. At present there are over 17 commercially available protocols with each yielding products with unique compositions and characteristics.¹³ Significant variations in PRP contents have even been reported within an individual patient over a two-week time period which further underscores the difficulty in grouping all PRP preparations into a single entity.¹⁴ Ultimately, the bioavailability of growth factors delivered as PRP will depend on individual patient characteristics, platelet concentration, levels of leucocytes and red cells, and method of activation, among other variables, as has been investigated in the February edition of *Bone & Joint Research*.¹⁵ Several classification systems have attempted to rationalise PRP contents.¹⁶⁻¹⁸ Unfortunately, current systems are not widely adopted and fail to appreciate the true variability of preparations. PRP must therefore be considered both individual and highly variable.

The regenerative characteristics of PRP are poorly understood

In addition to being highly variable, the influence of composition on the regenerative

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doi: 10.1302/2046-3758.53.
BJR-2016-0005

Bone Joint Res 2016;5:92–94.

characteristics of PRP is poorly understood. In particular, the effect of variations of cellular contents and the methods of activation on growth factor and cytokine profiles is not clear. Furthermore, the relationship between growth factor profile and biological activity and potency has not been defined. How these factors interact with co-delivered stem cells or purified cytokines in clinical settings is largely unknown.¹⁹

The optimal PRP formulation for specific indications

Therapeutic strategies should be based on understanding the pathological basis of each condition. Understanding the role of each growth factor in the development of specific disease processes will facilitate identification of therapeutic targets on which components of PRP may act, guiding appropriate use. This must include an appreciation of the evolving injury micro-environment with consideration to the timing of therapy delivery.²⁰ Many of the cytokines present within PRP act within opposing biological pathways; while some growth factors may be beneficial in certain applications, the same growth factors may be deleterious in others. For example, the pro-fibrotic effects of transforming growth factor-beta (TGF- β) may be beneficial for ligament and tendon healing,^{21,22} but negatively affect healing muscle.²³ Likewise, vascular endothelial growth factor (VEGF) has pro-angiogenic roles critical to muscle regeneration, but which are also detrimental to the healing of articular cartilage.²⁴ In the future, customised PRP preparations most suited to the specific indication may be developed. As with any biological treatments, optimal PRP formulations should be established and refined in pre-clinical studies before being applied to patients.²⁵

Current studies fail to characterise PRP and under-report methods

Unfortunately, many published clinical trials evaluating PRP fail to include sufficient experimental detail or report even the basic attributes of PRP formulations used, including platelet and leucocyte concentrations and the method of activation. This precludes interpretation of the exact nature of PRP formulations delivered (including growth factor profiles) in studies to date, prevents comparison between studies, and does not permit other investigators to replicate conditions. This is a particular challenge given the complexity of biological therapies and the wide array of preparation methods, protocols and methods of delivery now widely used.

In conclusion, we must encourage research that promotes a more scientific approach to the use of PRP. Each clinical scenario represents a unique dynamic biological microenvironment and the therapeutic solution should be specifically targeted for this. Studies should be 'hypothesis-driven' based on understanding the pathological basis of any given disease and the identification of

specific therapeutic targets on which PRP components may act. Full characterisation of platelet-rich concentrates will enable the most appropriate preparation to be used for each specific scenario and enable a more rational approach to allow for translation to clinical use. An investment in basic science research will ensure that patient safety is maximised and that only fully characterised and optimised formulations are evaluated in high-quality clinical studies, which are inevitably time-consuming and expensive. Ultimately, a renewed and comprehensive approach to our scientific understanding of PRP is required to guide the appropriate and effective use of these therapies in future.

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Funding Statement

- R. F. LaPrade reports funding received from Arthrex, Ossur, Smith & Nephew which is not related to this article.

Author Contributions

- I. R. Murray, Wrote the paper.
- R. F. LaPrade, Wrote the paper.

ICMJE conflict of interest

- None declared.

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