The decision to add PRP to my practice - a personal perspective

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Ansar Mahmood is a Consultant Orthopaedic Surgeon based in Birmingham with specialist interests including major orthopaedic trauma, sports and tendon injuries, post trauma reconstruction and regenerative medicine. He entered the field of regenerative medicine in 2010 while working with expert clinicians with an established background in the use of PRP in chronic tendon and inflammatory conditions. Ansar is the course director at the Academy of Regenerative Medicine, an instructor in Advanced Trauma Life Support (ATLS) and current President of the British Trauma Society (BTS).

I became interested in PRP about 14 years ago when faced with patients with recalcitrant pathology in the Achilles tendon or plantar fascia. With senior colleague support, I injected some with a 'golden serum'. What piqued my interest was that the exact mechanism was unclear but related to growth factors and inflammation that the platelets were good at optimising. Follow-up several months down the line showed they clearly felt it had worked when all previous treatments had failed, including steroids, manipulation, needling etc.

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When I took up my consultant post, I had been studying PRP for several years and felt I understood the basic science and the potential pitfalls of the available commercial systems. Due to UK restrictions and regulations, I had to make a decision to use something for research as well as for clinical application, so I set up a PRP lab at the Institute of Translational Medicine at the University of Birmingham and ran quantitative and qualitative analyses with Professor Harrison and Professor Grover. Following this, I researched the literature on the different PRP types and systems and chose a system to evaluate further.

In my naivety as a fresh consultant, I had originally decided I would learn all there was to learn about PRP from my lab and the clinical research data before I used it on patients. However, upon delivery of our first PhD student's thesis after four years of work on burns and graft take, I realised that this was a decades long journey. For the multiple areas I was interested in from wound healing, bone healing, cartilage and tendon regeneration, it was likely I would have retired before I ever had the opportunity of using these autologous biological therapies. I attempted to speed up my journey by visiting the heads of R&D of various commercial providers which gave me invaluable insight into how the different systems evolved and the findings that led to so much variation in the substrate they produced. Regenerative medicine as it has been coined for more than a decade is evolving at a rapid rate and the indications, systems and patient/clinician interest are also growing quickly.

However, this treatment intervention was not new and had in fact been around for about 20 years already. So why had it not found mass market appeal and why were there conflicting reports around its efficacy? I was initially hesitant about >>

using PRP therapy as I did not feel that the published evidence was sufficient to support its growing popularity. After conducting an extensive review of the evidence, attending conferences with the leading experts in regenerative medicine and understanding the basic science regarding PRP, it was clear to me that not all PRP was equal. There were big differences in the final delivered substrate and also variation in the pathology and patients receiving the treatment.

After almost a decade of interest, reading and study, I started treating patients initially with a 'reliable' PRP system and collected data on those patients in both the NHS and private sector. I have presented that data and continue to collect my and other clinician's data in our unit. We have found that being open and transparent with patients on what we don't know as well as what we do know about the treatments and explaining the reported outcomes, as well as our own data, has built trust and has helped the majority of our patients improve their pain and function. I am open with every patient and inform them that the area of 'Orthobiologics' is evolving quickly and that I would be surprised if I was delivering exactly the same treatments in a year's time.

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There is robust basic science in-vitro and a substantial amount of in-vivo work demonstrating the potential pathways and positive effects of PRP in different microenvironments. For orthopaedic clinical practice in joints and tendons, there are literally thousands of papers. There is no doubting the potential of these biological therapies but has this been translated into clinical practice? The answer to this is both yes and no. There are over 34 RCTs showing benefit and superiority of PRP to placebo, Hyaluronic Acid (HA) and steroid[1]. This is probably more evidence than is available for the majority of surgical procedures performed on our lists on a daily basis. However, there are also many trials showing no difference and occasionally inferior results of PRP. Understanding how this arises is fundamental.

Almost all the meta-analyses and RCTs involving PRP and other Orthobiologics involve significant heterogeneity in both the disease and the substrate used. There is often poor protocol reporting and this is driven by a lack of standardisation in what is expected to be in a particular injection. This has been well reported and addressed by Iain Murray *et al*[2].

Once the different cellular profiles of the various PRP systems are understood, the literature starts to make more sense and the basic science can inform clinical practice. Some of the emerging evidence is helping us shed light on the factors that improve outcomes:

1. Recent advances in our scientific understanding confirm which components in whole blood augment PRP's healing potential and which ones inhibit it. It is not all about platelets. The mononuclear cells and particularly monocytes appear to play an important role.

2. The components of an ideal PRP formulation for a target tissue are becoming better understood.

3. Reviewing the literature, experts can see why some studies showed that PRP was ineffective. The PRP used was far from an ideal system e.g. the recent JAMA publication of Kim L. Bennell *et al*[3] looking at knee OA. They used a system that produces an average concentration of platelets of 1.2-1.3 fold versus the systems that experienced practitioners use for osteoarthritis which is usually a minimum of 4-5 fold above the patient's baseline. The aim is to achieve a platelet dose of approximately $1x10^6$ platelets/microlitre as there is growing evidence that this provides superior outcomes.[4]

4. Because this optimal formulation has not been standardised to the pathology or to the individual patient, systematic reviews of the literature cannot exclude bias due to suboptimal formulations. Therefore, many reviews have inconclusive results.

Our understanding of how platelets function and how neighboring cells and plasma proteins influence their function has increased dramatically. We now know that red blood cells and neutrophils have an inflammatory and catabolic (degrading) effect within the treatment area and inhibit the healing process. In contrast, monocytes and lymphocytes have an anabolic (regenerative) effect within the treatment area and are likely to enhance the platelets' ability to heal[5]. This 'catabolic to anabolic switch' is likely to be different for each micro-environment we wish to influence and certainly requires more study and will be crucial in producing pathology customised regimes and protocols of PRP in the future.

The future of PRP may involve customised treatments such as:

- A dose of platelets large enough to create a healing response in a given tissue.
- Minimising red blood cells for most applications.
- Minimising neutrophils or allowing selection in some tissues.
- Maximising monocytes in most tissues.
- Maximising lymphocytes in tendon but perhaps less so in cartilage.

Many PRP systems that produce poor quality injectate formulations are still on the market today. For example, there are over 40 PRP processing systems/protocols mentioned in the literature, but fewer than five can remove >99% RBCs from the PRP sample. Now that the understanding of the cellular content of PRP has improved, newer generation PRP systems (with more favorable formulations) are being developed. When these systems are used, outcomes are likely to be more favourable. Standardisation and reporting into biologic registries and 'big data' collection will likely lead to a better understanding of what works best.

PRP Treatment Method in my hands in January 2022

Typical patient: Kellgren Lawrence Grade 1-3 knee OA still of working age with knee pain. Previous knee arthroscopies in the past. No mechanical symptoms and BMI less than 30. (Shorter term results in higher BMI although patients do usually respond).

All options discussed including:

- Non-invasive: Exercise/physio, analgesia, bracing already undertaken.
- Minimally Invasive: Steroid, HA, PRP and potentially advanced biologics including plasma and progenitor cell products (this is an escalation therapy in our practice and not first line).
- Invasive: Surgery usually starting with joint preservation options if suitable.

If the patient elects for PRP, informed consent is started at consultation. A digital consent and PROMS form including VAS pain scale, OKS & WOMAC are sent electronically. The patient has an ultrasound guided injection for knee OA. I currently inject approximately 4-5 mls of injectate of a leucocyte poor high purity (0.1% RBC) made from 22 mls of whole blood with a yield efficiency of approximately 85-90%. This is spun at 1,500 RCF (Relative Centrifugal Force) for 10 minutes and then concentrated to approximately 5x concentration of platelets. RBCs are almost completely eliminated, leucocytes are 95% eliminated but approximately 80% of the monocytes are retained.

I always use ultrasound guided injections for the best results as it has been shown that biological therapies must be delivered precisely to the appropriate anatomic site. There are quantitative and qualitative clinical studies showing superior outcomes in patients where ultrasound is used. Patients are usually offered three injections as current evidence suggests that for results lasting 12 months and beyond this is the best protocol. We are currently validating this. ■

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