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Platelet-Rich Plasma Therapies in Lateral Epicondylitis: Are we Asking the Right Questions?

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Introduction

Greater understanding of the pathophysiology underlying musculoskeletal conditions provides the opportunity for more targeted, advanced treatment options. When lateral epicondylitis was first described by Runge in 1873 it was thought to represent inflammation of the common extensor origin of the forearm [1]. This has been subsequently disproved histopathologically, and the term epicondylitis is now itself a misnomer [2-4]. It is instead a form of tendinosis, resulting from repetitive stress-mediated degeneration of the common extensor tendon origin [5,6]. The formation of micro-tears triggers a complex collagen-mediated histopathological reaction; known as angiofibroblastic hyperplasia [2-5].

Traditionally, lateral epicondylitis has been treated conservatively with good outcomes in 80% of patients [7,8]. Conservative treatment involves rest (avoidance of aggravating activities and behaviour modification), physiotherapy, bracing, analgesia and non-steroidal anti-inflammatory medications [9,10]. For patients refractory to conservative treatment, injections with corticosteroids are still routinely used. Ultimately, patients not responding to non-operative measures may require surgical intervention [5,9]. A variety of procedures (open or arthroscopic) have been described, with no clear consensus established on a gold-standard operation [5].

Greater pathophysiological understanding has promoted the use of a number of alternative modalities focused on augmenting soft tissue healing. These include extracorporeal shock wave therapy, laser therapy, botulinum toxin injection, topical nitrates, autologous blood injection and finally, Platelet-rich Plasma (PRP) injection [5,11]. These therapies have a theoretical advantage over corticosteroids, due to the lack of evidence for inflammation in lateral epicondylitis. Given that the evidence base for individual surgical procedures remains weak, alternative injections may also prove beneficial in reducing the number of refractory cases requiring surgery.

PRP is derived from the centrifugication of autologous blood, resulting in higher platelet concentrations than that of the original sample [11]. The rationale behind its use lies in its potential ability to provide growth factors to the relatively avascular diseased tendon, thus promoting tissue healing and tendon regeneration [11]. PRP has gained a significant amount of attention in orthopaedic and sports medicine communities in the past decade, largely due to the promising results of pre-clinical laboratory studies [5,11,12]. In practice, PRP is applied by single or multiple injections to the area of maximal tenderness [5].

While PRP therapy for tendinopathies has attracted significant scientific exposure in recent years, fundamental inconsistencies still exist within the literature. Authors continue to question the efficacy of PRP for refractory tendinopathies, while leaving a number of key questions unaddressed. By shifting our focus to answering these questions, we may improve our understanding of the clinical role of PRP therapy. We will attempt to highlight a number of the issues within the current literature; including variable preparation methods and PRP solutions, inconsistent control group interventions, the use of adjunctive physiotherapy, and its comparison against autologous blood injections.

PRP preparations

One key shortcoming found across studies analysing the efficacy of PRP is significant variability between preparation methods and final platelet concentration. Significant differences have been demonstrated between the White Blood Cell (WBC) and growth factor levels produced using various commercial PRP separation systems [13,14]. Studies have differed in the quantities of PRP injected (ranging from 1.5 mL to 3.5 mL), either alone or in combination with variable amounts of local anaesthetic and/or epinephrine [15-19]. The number of injections given and time intervals between injections also varies between studies.

At present, PRP preparations differ on the basis of their platelet concentration [20-23]. Further, the relative concentrations of different growth factors, the method of platelet activation (exogenous vs. endogenous), the degree of WBC contamination and PRP storage conditions are all implicated to affect the healing potential of PRP injection, and none are standardised across studies [20,21,23]. Additionally, the inter-person variability in growth factor concentration has been demonstrated to be as high as 50% between samples obtained from individuals in the same study [21].

While one might assume that increasing the platelet concentration of the PRP injection would promote greater tissue healing and better outcomes, this has not been demonstrated in research and the optimal platelet concentration has not been established. Yamaguchi et al. (2010) conducted an animal study focused on the effect of different platelet concentrations on intestinal anastamotic healing [24]. Perhaps counter-intuitively, they found that their low platelet concentration group exhibited the highest levels of wound healing, whereas higher concentrations were found to inhibit wound healing in relation to their control. This suggests that lower platelet concentrations than initially thought may provide the best therapeutic results. Research on optimizing platelet concentrations in PRP, however, is currently lacking and variation between clinical trials may skew results and mask the genuine efficacy of an optimized PRP injection.

Controversy also exists over the potential benefit or harm of WBC contamination of PRP preparations. Some authors argue that higher WBC concentrations may provide antimicrobial action and increase the concentrations of growth factors present [21]. Others have argued that WBC contamination will augment inflammation and pain and further impede tissue healing [19]. No consensus has been established within the literature on the subject.

A recent Cochrane review [11] reported that "currently there is no consensus regarding standardisation for research or clinical use. There are several preparation methods for platelet products, which are likely to be a source of heterogeneity for the assessment and comparison of the effectiveness of PRT". It goes on to recommend that standardisation of PRP preparation methods is required for the reliable assessment of its efficacy.

Control groups

The lack of congruency between authors on suitable control groups additionally limits possible comparison and clinical application of their findings. Many studies have used either corticosteroid or local anaesthetic (typically bupivicaine) injections as their control arm [16,18,25,26]. However, both have come under recent criticism and are suggested to generate worse long-term clinical outcomes than conservative treatment alone. Lehner et al. (2013) reported on the detrimental effects of bupivicaine on tendon tissue in animal studies, demonstrating that bupivicaine injection increased the tendon vulnerability to injury and overload stress [27]. The use of corticosteroid injections to treat various tendinopathies, while still commonplace in clinical practice, has been repeatedly challenged by authors [28]. It is logical to predict that an anti-inflammatory substance should confer no benefit in the treatment of a non-inflammatory, degenerative condition. Coombes et al. (2010) substantiated these attitudes by performing a systematic review on the efficacy and risk associated with the use of corticosteroid injections in the treatment of tendinopathies [29]. They concluded that while corticosteroids improve symptoms in the short-term following injection, they resulted in worse intermediate and long-term clinical outcomes than no intervention. As these control groups cannot be validated, the true effect of PRP injections may be exaggerated within these studies.

Adjunctive physiotherapy

No agreement has been reached on the efficacy of adjunctive physiotherapy or exercise following PRP injection [30]. Given the mechanism of PRP therapy it would seem logical to prescribe a period of relative rest to allow sufficient healing of the affected tendon, followed by a stretching and strengthening programme to improve functional outcomes. The precise amounts of time allocated to each phase, as well as any benefit provided by initial rest have not been analysed. Further, significant variability and incomplete reporting exists between studies [15,18,25,26]. This further shrouds the efficacy of an optimized PRP therapy in lateral epicondylitis.

PRP vs. autologous blood injections

Of all of the alternative therapies proposed for the treatment of refractory tendinopathies, PRP has received the greatest amount of attention in orthopaedic and sports medicine communities. Based on promising pre-clinical data, it has become a highly attractive potential treatment modality. As such, research in alternative injection therapies has focused on comparing either PRP against control interventions or PRP against autologous blood injections. Research focused on the efficacy of autologous blood against control interventions is sparse and of lower quality. However, PRP has not been definitively proven to be more efficacious in the treatment of lateral epicondylitis than autologous blood [15,19,31,32]. Three systematic reviews comparing the modalities have concluded that the evidence available is insufficient to justify the use of PRP over autologous blood [17,30,33]. In theory, this may relate to the healing benefit conferred by lower platelet concentrations than initially thought.

This is of great significance when considering the cost efficacy of the individual modalities. It is estimated that PRP therapy for an individual patient costs an average of $1000 (USD) [16]. In contrast, autologous blood injection requires little more than a syringe and five minutes of a physician's time. Given that it has been shown to hold equivalent clinical outcomes to PRP and provide significant symptomatic improvement over no intervention [32,34], autologous blood injection represents a much more cost effective treatment option. Until PRP can be definitively proven to be more efficacious, it would seem sensible to focus research on establishing the clinical role of autologous blood in lateral epicondylitis.

PRP for other conditions

Although lateral epicondylitis has been the focus of this editorial, PRP therapies have become widely used for a variety of acute and chronic musculoskeletal injuries [11,12,22]. Lengthy recovery times and residual symptoms, combined with patient demand for an expedited return to activities has increased the popularity of PRP dramatically in the past decade. PRP therapies used can be broadly segregated into a primary intervention for tendinopathies (eg. medial/lateral epicondylitis, Achilles and patellar tendinopathy) or an augmentation procedure for surgical intervention (eg. rotator cuff repair, subacromial decompression, ACL reconstruction and repair of Achilles tendon rupture) [11]. Overall, no significant functional improvement has been consistently demonstrated in favour of PRP therapies used for either purpose [11]. Short-to-medium term pain reduction in favour of PRP has been demonstrated by a number of authors, although is challenged by others [11]. PRP has not been shown to increase the risk of adverse events over controls [11]. The recent Cochrane review reported that "the available evidence is insufficient to indicate whether the effects of PRT will differ importantly in individual clinical conditions [11]. All areas of PRP research are plagued by the same shortcomings as for lateral epicondylitis research. Standardisation of preparation methods and follow-up protocol across studies is required to significantly advance our understanding of PRP's clinical role for a variety of musculoskeletal conditions.

Conclusions

A number of unanswered questions continue to exist relating to the use of PRP therapy for refractory tendinopathies. The lack of consensus over PRP preparation methods and equipment, the frequent use of inappropriate control interventions, and the poorly established role of adjunctive physiotherapy limits the amount of comparison possible between studies and weakens the evidence supporting the clinical use of PRP for lateral epicondylitis. Additionally, the focus of research on PRP therapy has distracted attention away from autologous blood injection studies. Despite being reported to hold equivalent clinical outcomes and being significantly more cost

effective, its clinical role remains obscure. We further recommend that future research focus on establishing the optimal concentrations of platelets, growth factors and WBCs in PRP preparations. Clinical trials should avoid the use of corticosteroid or bupivicaine as control interventions and should attempt to define the optimal programme of adjunctive physiotherapy.

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