The State of the PRP Nation

Platelet-Rich Plasma (PRP) therapy for equine orthopedic conditions

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Platelet-rich plasma (PRP) was originally used to augment mandibular bone repair; however, in recent years, PRP has become increasingly used for the treatment of a wide range of musculoskeletal conditions, including tendon, ligament and joint injuries, skeletal muscle healing and wound repair; verging on a universal treatment for orthopedic conditions. The rationale for PRP use is that these concentrates provide high levels of growth factors contained within the alpha granules of platelets (primarily, platelet-derived growth factor, transforming growth factor beta, and vascular endothelial growth factor) that stimulate reparative activities of host cells at sites of administration, beyond the stimuli generated by endogenous host responses. This issue is not trivial, given that many traumatic injury sites are exposed to platelet aggregation and degranulation following hemorrhage.

PRP is conventionally produced by two-stage centrifugation; an initial slow-speed spin sediments the RBCs and allows collection of the plasma fraction that contains platelets and WBCs. A second centrifugation at higher speed concentrates or pellets the platelets from the plasma sample. The efficiency of platelet concentration and exclusion of white blood cells from the PRP preparation can be controlled by regulating the speed and extent of the second centrifugation step, and by altering the amount of plasma that is decanted from the second centrifugation step. A more rapid spin will increase the PRP concentration, but the pellet is also likely to contain more WBCs. The objective is to increase platelet concentrations in the final prep to greater than 1000 x 10^3 platelets/μl (approximately 5-fold increase in platelet concentration) although the actual concentrations achieved vary greatly between samples.

Several commercial centrifuges and receptacles are available for the in-house production of PRP. Apart from providing a standardized protocol for PRP production, the commercial systems also limit the manual handling and transfer of the sample that's required and so reduce the risk of sample contamination. Accepting these obvious advantages, recent independent analyses of the 'PRP' products generated by commercial protocols are disconcertingly inconsistent, to say the least [1,2]. The value and/or liabilities associated with leucocyte 'contamination' are very poorly defined [3,4]. Further, the need for, and mechanisms of, activating PRP vary widely from study to study, making any objective assessment of PRP's utility extremely challenging.

"…the assessment of PRP's efficacy is fraught by an almost total inconsistency in PRP preparation and administration between studies, in both the human or veterinary fields." Dr Jamie Textor [5].

Much of the inter-study variation mentioned above revolves around whether (or not) the platelets are activated (implying degranulation and release of bio-active factors), the method of activation (freeze/thawing, thrombin or calcium re-supplementation) and the actual PRP agent administered (soluble PRP, a clotted PRP gel or the liquid releasate that is formed after platelet clot formation). These variables are critical for assessing clinical outcomes and consistent and reliable application of equine PRP. Equine platelets are not significantly activated by the shear forces or turbulence generated by injection or by exposure to exogenous equine thrombin [6], making any accurate determination of 'activity' after administration very difficult to assess. To make matters even more complex there is no clear relationship between platelet concentrate numbers and the concentrations of growth factors believed to mediate PRP's therapeutic effects.

Does PRP work for tendinopathy in people? People aren't horses, (or dogs or cats), but outcomes from clinical studies in people benefit the veterinary community because the numbers of patients are usually much higher, quantitative outcome assessments are validated and established and the statistical power of the outcomes are, consequently, stronger. Conducting meta-analyses (and, more recently, meta-meta-analyses) of PRP clinical outcomes has become something of a cottage industry in the biomedical literature [4,7-16], as a consequence of the rise of evidence-based medicine practices, commercialization of PRP production, the relatively tolerant regulatory oversight of biologic agents. The results of these meta-analyses are not all that encouraging. Perhaps the most disappointing aspect of these summary analyses is the very small number of clinical studies that pass muster as being appropriately controlled randomized, and unbiased.

Rotator cuff syndrome is a major cause of tendinopathy-associated disability in people, and a very challenging condition to treat. It is analogous, in several respects, to suspensory branch desmitis/sesamoiditis in horses, since the pathology develops at tendon-bone interfaces. Based on the collective analyses of three meta-analyses, there is little evidence to support the use of PRP for treating tendinopathy associated with rotator cuff syndrome in people, apart from small, mild lesions that carry a relatively good prognosis anyway [8,10,15].

Achilles tendinopathy in people is, perhaps, most similar to SFD tendinopathy in performance horses. The results of PRP administration for Achilles tendinopathy in people are mixed. A randomized, placebo-controlled clinical trial involving 54 patients [19] found no clinical differences between the PRP-treated and saline control groups. The outcome measures in this study were by patient survey follow-up only; there were no quantitative analyses of functional

outcome or blinded clinical evaluations. Nevertheless, based on the patients' own perceptions, PRP was not more effective than the notorious placebo effect of saline. Similarly underwhelming results were reported by Schepull et al [20], in cases of Achilles tendon rupture. However, PRP clot implantation during surgical reconstruction of Achilles tendon rupture [21], resulted in clear improvements in recovery rates, function and tendon appearance. A recent meta-analysis of PRP administration in over 1000 Achilles tendinopathy cases showed therapeutic benefits in patients who received leucocyte-rich forms of PRP (but not leucocyte-poor PRP), despite the concerns regarding the inflammatory consequences of WBC 'contamination' [4].

Does PRP work for tendinopathy in horses? PRP has been used in an experimental model of equine SDFT injury, where a core lesion is created surgically, rather than by collagenase injections [21,22]. The core defect crated in this model heals remarkably quickly and well in control animals, unlike SDF tendinopathy seen in clinical cases. A single inactivated PRP injection was administered 7 days after the injury and the effects of PRP (vs. saline) were assessed after 6 months. The tendons treated with PRP were significantly more cellular, had greater collagen and glycosaminoglycan contents, were more highly vascularized and exhibited better tissue organization than the controls. Accepting the dubious value of increased GAGs and vasculature, the PRP-treated tendons were also approximately 50% stronger than the controls under tensile loading to failure.

A single PRP injection was used to treat nine clinical cases of severe mid-body suspensory desmitis in Standardbred racehorses [23]. All nine horses returned to racing approximately eight months after injury, after a controlled rehabilitation program, and all nine raced for at least two years, making as many starts as a control cohort of nine uninjured horses. Accepting the small number of cases included in this study, the outcome is impressive given the severity of the desmitis lesions in these horses. Injecting PRP into suspensory ligament branch desmitis/sesamoiditis lesions in TBD yearlings prior to training significantly increased the number of these horses that raced as 2 year-olds (12 of 20 cases), compared to saline-injected horses (5 of 19), although this difference did not carry over into the 3- and 4-year-old seasons [24]. Somewhat depressingly, the increase in 2 year-old starts did not translate to any significant increase in race earnings.

PRP has also been used as a bio-active vehicle for allogeneic adipose-derived cells to treat clinical SDF tendinitis in 19 performance horses [25]. 17 of these horses returned to their previous level of activity within 24 months. There were two recurrent injuries in the group. Current experimental data suggest that the cell-associated component of this therapeutic strategy has greater influence on outcome than the PRP [26].

Does PRP work for osteoarthritis in people? There have been a number of studies over the past several years, addressing the value of PRP injections to treat the clinical signs associated with knee and hip OA in people, and these primary studies have spawned several meta-analyses [7,9,11-14,16,17]. The majority of these clinical studies were carried out in patients >50 years of age, presumably waiting for their total joint replacements. Consistently, PRP has been more effective than hyaluronic acid or saline in controlling clinical signs and dysfunction in knee OA. Impressively, these effects persist for up to 12 months. The efficacy of PRP in hip OA is much less clear.

Does PRP work for osteoarthritis in horses? Self-evidently, we ask far more of our performance horse patients than might be expected of most late middle-aged people, so the reported benefits of PRP in knee OA patients might be less evident in horses. There are few informative equine studies on the value of PRP in equine osteoarthritis, to date. A few studies in healthy horses have confirmed that intra-articular PRP injections induce a mild and transient inflammatory response that resolves within 7 days [27]. PRP has little or no effect on 'anabolic' or inflammatory cytokine levels in otherwise normal synovial fluid [27]. Alicia Bertone's group at OSU assessed the responses of 40 clinical OA cases to an Autologous Protein Solution (APS) that was generated by a two-stage centrifugation protocol but which had characteristics more consistent with IRAP than PRP [28]. Accepting this, the cases injected with APS responded significantly better than the control cases, becoming less lame and increasing range of motion in the affected joints. A recent publication from LSU used kinematic outcomes (without directly addressing lameness per se) to assess the comparative effects of intra-articular anesthesia and PRP on lameness [29]. Only 4 of the 10 horses that responded to IAA also responded to PRP injections, and the 'responders', although improved, were not sound after the injections (Dr. Mandi Lopez, personal communication).

It is highly likely that more studies addressing the clinical value of intra-articular PRP injections for equine OA will appear over the next few years and provide some clarity on the value of this biologic for managing equine arthritic conditions.

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