THE USE OF PLATELET-RICH PLASMA IN A DAILY PRACTICE

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ABSTRACT

Platelet-rich plasma (PRP) is an autologous biologic treatment composed of the patient's plasma containing growth factors released from platelets and endogenous fibrin scaffold. The rationale behind its use is to stimulate the natural healing cascade and regeneration of tissues by a supraphysiologic release of platelet-derived factors directly at the treatment site without the risk of immune rejection or disease transmission. In joints, platelet growth factors appear to produce a wide range of effects in the joint environment. Osteoarthritis (OA) is one of the conditions most commonly treated with PRP injection. We undertook a study where we evaluated the use of PRP produced with the Companion CRT PurePRP® Kit, compared to a control group (receiving a saline injection), in polices working dogs with bilateral hip osteoarthritis. Our results showed that intra-articular (IA) PRP had a beneficial effect in police working dogs with bilateral hip OA, even in cases of severe OA. The improvement was observed in all of the considered scores, in some cases starting at the first follow-up (+15d). Many scores in the PRP group were significantly better than those of the control group up to the +120d follow-up and, in the case of the pain severity score, up to the last follow-up (+180d).

Keywords: Platelet Rich Plasma (PRP), Osteoarthritis, Platelets, Canine, Growth Factors

Platelet-rich plasma (PRP) is an autologous biologic treatment composed of the patient's plasma containing growth factors released from platelets and endogenous fibrin scaffold. The rationale behind its use is to stimulate the natural healing cascade and regeneration of tissues by a supraphysiologic release of platelet-derived factors directly at the treatment site, without the risk of immune rejection or disease transmission.

All healing processes go through three phases: inflammation, proliferation, and remodelling. After an injury, which starts the inflammation phase, platelets are on the front line and have a critical role in mediating healing by releasing growth factors from their α granules. The α granules have a crucial role in tissue regeneration and can release more than 800 different proteins, including serotonin, adenosine, dopamine, histamine, adenosine diphosphate, adenosine triphosphate, and catecholamines. Growth factors also signal cells to proliferate and influence maturation, differentiation, and tissue repair. They include insulin-like growth factor (IGF-1), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), vascular endothelial growth factor (PDGF), and basic fibroblast growth factor (b-FGF). When activated, platelets also release a group of biologically active proteins that bind to the transmembrane receptors or their target cells, which leads to the expression of gene sequences that promote cellular recruitment, growth, and morphogenesis. Their administration right at the lesion site promotes a supraphysiologic release of these products directly at the intended site of action, signalling cells to proliferate and influence their maturation, differentiation, and tissue repair. As a whole, PRP is seen as able to control the activities of different cell types that target multiple biological processes, such as apoptosis, extracellular matrix synthesis, modulation of angiogenesis, and inflammation.

Several studies in animal models have demonstrated the efficacy of PRP in accelerating the healing process after injuries in muscle, ligament, joints, and

tendons. In joints, platelet growth factors appear to produce a wide range of effects in the joint environment, targeting multiple pathways of the joint metabolism. It has chondroinductive effects, with TGF-β contributing to chondrocyte phenotype expression and mesenchymal stem cell chondrogenic proliferation. IGF-1 also has anabolic properties in cartilage regeneration. PDGF has mitogenic action, influences chondrocyte proliferation and proteoglycan. b-FGF stimulates the migration of fibroblasts and collagen synthesis. They also exert autocrine and paracrine functions, promoting angiogenesis, extracellular matrix and aggrecan production, collagen synthesis, and influencing tissue regeneration. PRP induces a significant decrease of MMP-13, MMP-9, and MMP-2 levels, decreases the chondrocyte apoptosis cascade while increasing hyaluronan synthase-2 expression in chondrocytes, thus enhancing hyaluronan secretion and contributing to joint homeostasis. It alters the expression of specific target genes, particularly during the early stages of remodelling. Some reports also present a direct analgesic effect through the augmentation of cannabinoid receptors CB1 and CB2.

The term PRP is loosely used, which has raised some confusion and apparently contradictory results on its use and effects. Different types of PRP exist, with different compositions and properties, classified according to its profile regarding leukocyte and fibrin levels: pure platelet-rich plasma leukocyte, and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte and platelet-rich fibrin. Many studies do not accurately characterize the platelet product being reported on, which further adds difficulties to compare different studies' results. Since platelet products can present such a variety of preparation steps and characteristics, a group of experts outlined the minimum reporting requirements for clinical studies evaluating PRP. This should be standard information we look at when reading about PRP. There is a belief that red blood cells and neutrophils should be reduced due to their inflammatory role, as the effect of mononuclear cells presence remains largely unknown. Some authors attribute the deleterious effects to protease and free radicals released by these cells, increasing the catabolic cascade. In contrast, PRP without leukocytes has been described in humans as having better results when treating knee OA than leukocyte rich-PRP. Also, in humans, the concentration of inflammatory cytokines in PRP is correlated with leukocyte concentration.

PRP is prepared from autologous, anticoagulated whole blood, with a 3-8-fold concentration of platelets. Human studies show that the ideal PRP product should have a 4 to 7-fold increase in platelets. Increasing platelet numbers beyond this point may not add any benefit or may even be detrimental, as they can be a source of inflammatory cytokines and potentially prevent tissue healing. Very large volumes of PRP might also have a cytotoxic effect on healing grafts. Commercial kits are available for the production of in-house PRP, with variable characteristics. Blood collection is usually performed from the jugular vein, followed by a double spin procedure. The first spin is typically slow to avoid spinning down platelets, whereas the second spin is fast to spin down the platelets. With this procedure, after the first spin, platelets are mainly concentrated right on top of the buffy coat. Excessive centrifugation speed may damage platelets and produce a bad quality PRP. Additional care is necessary to guarantee sterility throughout the process. For these reasons, closed commercial kits, with a controlled and standardized production protocol, secure the procedure sterility and final product characteristics and quality.

Osteoarthritis is one of the conditions most commonly treated with PRP injection. There are several reports regarding the use of PRP in human OA. Three injections proved to be significantly more efficient than a single injection of hyaluronan to reduce knee pain and stiffness while improving function. Even a single injection has produced better effects than a placebo, with effects being present at six months to 1-year post-injection. In general, and in the long term, PRP seems to be more effective than hyaluronan or other therapeutics. Better results seem to be observed in younger, more active patients with a lower degree of cartilage degeneration than those with more advanced OA. In dogs, a single PRP injection has resulted in clinical improvements for 12 weeks, in some cases without progression of radiographic signs. Through this period, radiographic scores were the same as assigned before treatment. Multiple injection protocols have also been described, providing improvements in ROM, pain, lameness, and kinetics. Authors associated this response to treatment with the anti-inflammatory

activity of PRP rather than any effect on tissue anabolism or catabolism. It has also been used as a part of surgical protocols, leading to significantly better gait performance in the postoperative period. Additional reports conducted in animal models show that PRP significantly suppresses morphological and histological changes of OA, increasing neochondrogenesis and proteoglycan content in the extra-cellular matrix.

No ideal number of injections or intervals is currently set, and for that reason, the number is usually based on clinical experience or a desired improvement level. Generally, patients are re-examined 2-6 weeks after the procedure to evaluate pain, function, the injection site and discuss concerns and future management course. Post administration withhold of NSAIDs is recommended for ten days and, preferably 3-6 weeks after the procedure, due to a theoretical assumption that they may impede or delay tissue healing and may even produce fibrosis. PRP side effects are usually local and transient, consisting of injection pain, local inflammation of short duration, and reaccumulation of effusion, taking 2-10 days to resolve.

We undertook a study where we evaluated the use of PRP produced with the Companion CRT PurePRP® Kit, compared to a control group (receiving a saline injection), in police working dogs with bilateral hip OA. Animals received two intra-articular administrations of 2ml of PRP per hip joint, 14 days apart. On treatment day (day 0), and on days 15 (+15d, before the second IA PRP administration), 30 (+30d), 90 (+90d), 120 (+120d), 150 (+150d), and 180 (+180d) after the initial treatment, a copy of the Canine Brief Pain Inventory, the Canine Orthopedic Index, the Liverpool Osteoarthritis in Dogs, and the Hudson Visual Analogue Scale was completed by the handler. We compared the results of each clinical metrology instrument between groups. We also conducted a survival analysis to determine treatment duration and the influence of interest covariables (age, sex, body weight, breed, and OFA score) on the results.

Our results showed that IA PRP had a beneficial effect in police working dogs with bilateral hip OA, even in cases of severe OA. The improvement was observed in all of the considered scores, in some cases starting at the first follow-up (+15d). Many scores in the PRP group were significantly better than those of the control group up to the +120d follow-up and, in the case of the pain severity score, up to the last follow-up (+180d). In all considered scores, the mean number of days animals in the PRP group took to return to the initial evaluation levels was significantly higher than in the control group. The model build with the Cox regression showed that treatment was the covariate with a more significant impact over the observed changes, as it had a significant difference over control in all scores. Dogs in the control group always had an increased probability of returning to the initial evaluation levels, varying from a 1.82 (with pain severity score) to a 10.72-fold (with gait) probability for this event to occur. Few other covariates had an impact on the model. With pain severity score, increasing bodyweight corresponded to slightly higher risk (1.06-fold). OFA grading influenced the quality of life and overall canine orthopedic index scores, with dogs with severe OA showing a 2.96 and 3.02 probability of returning to the initial values compared with dogs with moderate OA. This finding stresses the relevance of early intervention, as it leads to a better outcome.

From a clinician perspective and our personal experience, you should consider using PRP and the Companion CRT PurePRP® Kit for several reasons:

- PRP has several well documented positive effects on multiple conditions that can be added to our treatments, regardless of the nature of your practice.
- It is a closed and safe system, which delivers a standardized and well-characterized PRP.
- It removes leukocytes and red blood cells, eliminating their undesired effects at the treatment site.
- It is a validated system, with several papers published on its use.
- It is made up of the patient's own cells, which allows not only for decreasing pain levels, but has a disease modifying role through the remodelling of tissues and pain pathways, with long-lasting effects.

For those reasons, you should consider treating patients early on and look at PRP as a possible first treatment rather than a last-line resort.

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