



Current Evidence on Using Platelet Rich Plasma as a Therapeutic Modality for Veterinary Orthopedic Conditions

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ABSTRACT

This review evaluates the findings of available clinical literature on the use of platelet-rich plasma (PRP) to develop evidence-based recommendations for treating various musculoskeletal issues that arise in veterinary practice. The use of PRP-based treatments for various orthopedic conditions is rapidly evolving as a promising treatment modality; however, its true effectiveness has yet to be elucidated. Application of PRP has been reported in humans for a variety of orthopedic conditions. Although the majority of the veterinary literature on PRP reports its use in equine patients, there is a dearth of evidence addressing its use in canine patients. Nevertheless, evidence of the efficacy of PRP has appeared to be highly variable depending on its specific indication, particularly in musculoskeletal disorders. This review aims to present the available information on the efficacy of PRP therapy in veterinary orthopedic conditions and describes factors influencing its use, the limitations of PRP therapy, and future directions of PRP research and therapy.

Keywords: Musculoskeletal diseases, Orthopedic, Platelet-rich plasma, Veterinary

INTRODUCTION

Autologous platelet-rich plasma (PRP) is a biological preparation made from the patient's own plasma that contains a platelet concentration exceeding the baseline values of the whole blood. The use of a patient's own biological materials, such as PRP or plasma rich in growth factors, for tissue healing is a welcoming and alternative therapeutic approach with fewer side effects and lower cost, in comparison with other techniques. Induction of hemostasis, production of anti-inflammatory cytokines, and release of growth factors at the injured sites are the factors influencing the use of blood-derived compounds intensively in the clinical field (Alsousou et al., 2009; Fortier et al., 2011). Owing to the release of cytokines and other growth factors after degranulation, platelets play a key role in the inflammation and healing process (Garbin and Olver, 2020). The PRP secretes several growth factors (Figure 1) at the injured site and promotes mitogenesis as well as angiogenesis in the tissue (Eppley et al., 2006; Filardo et al., 2013; Hsu et al., 2013). These growth factors include platelet-derived growth factor, transforming growth factor- β 1, transforming growth factor- β 2, vascular endothelial growth factor, basic fibroblastic growth factor, and epidermal growth factor. In addition to these factors, PRP contains adhesion molecules that promote bone formation. These molecules include fibrin, fibronectin, and vitronectin (Marx, 2001).

Given its regenerative properties, PRP has been applied in a wide range of clinical applications, including musculoskeletal injuries. A considerable number of recent studies have shown PRP to be efficacious in managing many different orthopedic conditions and soft tissue injuries by going beyond its limited uses in dentistry and maxillofacial surgical interventions (Dragoo et al., 2012; Abrams et al., 2013; Filardo et al., 2013). Several studies have also documented the efficacy of PRP for the management of osteoarthritis (Kon et al., 2011; Filardo et al., 2012; Franklin and Cook, 2013; Khoshbin et al., 2013) as well as soft tissue healing (Dragoo et al., 2012; Dragoo et al., 2014). Platelets recruit, stimulate, and provide a scaffold for stem cells, hence the synergistic effect of PRP with stem cell therapy also has been documented in cartilage, bone, and soft tissue healing (Del et al., 2008; Dohan et al., 2008; Drengk et al., 2009; Mishra et al., 2009; Xie et al., 2012; Broeckx et al., 2014). *In vitro* studies demonstrated that PRP can promote the synthesis of proteoglycan and type II collagen, which are important for the structural organization of cartilage framework while down regulating inflammatory mediators, such as interleukin-1 (IL-1) (Smyth et al., 2013; Zhu et al., 2013; Kazemi and Fakhrajou, 2015). Apart from cartilage repair, PRP promotes repair of damaged tendons which tend to heal slowly after injury (Anitua et al., 2007). Despite these promising results, some studies have disclosed that the addition of larger concentrations of PRP induces a higher rate of apoptosis assuming that a higher concentration of growth factors to the cell may have a detrimental rather than a beneficial effect (Dhillon et al., 2015).

Musculoskeletal disorders are the most common consequences of physical overstrain or trauma in athletic humans as well as animals, which has a negative effect on physical performance and ultimately the quality of life. Regenerative therapy for racehorses is a rapidly growing field of research due to its potential substantial economic impact on the horse

industry. In fact, the speed of healing is a crucial factor in degenerative joint diseases and is a priority in veterinary research both for the quality of life of horses and a rapid return to competition. Evaluation of new treatments for musculoskeletal injuries in horses could benefit both equine and human medicine hence racehorses can serve as a valuable large animal model for evaluation of new human therapeutics (Frisbie et al., 2006).

This review aims to present the available information on the efficacy of PRP therapy in veterinary orthopedic conditions as well as factors influencing its use, the limitations of PRP therapy, and future directions of PRP research and therapy.

Knee osteoarthritis

Osteoarthritis is the most common form of arthritis in humans and animals. Osteoarthritis affects the entire joint, including the cartilage, tendons, synovial fluid, synovial membrane, and bone. Several animal studies on osteoarthritis characterized the degeneration of the cartilage and soft tissues, hypertrophy of bone at the margins, as well as changes in the synovial membrane and fluid viscosity (Vaughn-Scott and Taylor, 1997; Pasquini et al., 2007; Wijekoon et al., 2019). As the cartilage continues to wear off and deteriorate completely, it causes friction between the bones, which leads to inflammation, thickening of soft tissues, and loss of mobility of the joint (Pasquini et al., 2007). The treatment of knee osteoarthritis adopts both surgical and non-surgical options; however, nonsurgical treatments have recently captured greater attention. Most of the current treatment modalities for osteoarthritis focus on treating the symptoms, leading to an increase in disease-modifying treatments, such as PRP. The PRP is an efficient treatment option for osteoarthritis in numerous species due to its potential anabolic and anti-catabolic effects and the ease of preparation (Mifune et al., 2013; Carmona et al., 2016; Moussa et al., 2017). Amongst the several different options, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying osteoarthritis drugs (DMOADs) (Wijekoon et al., 2019) which are used to relieve pain while regenerating the tissue, the use of PRP has emerged as a novel treatment method. Serial intra-articular PRP injections could decrease the pain while increasing articular function. The studies conducted on horses have demonstrated that injection of autologous adipose tissue mixed with PRP can be safely performed and is well-tolerated (Benbo et al., 2016). Previous studies on the use of PRP in racing horses for the treatment of degenerative joint disease have shown promising clinical outcomes due to increased mesenchymal stem cells proliferation (Figure 2), enhanced chondrogenic differentiation, and improved cartilage regeneration (Mishra et al., 2009; Rubio-Azpeitia and Andia, 2014; Atashi et al., 2015). It has been reported that an autologous protein solution and a platelet-derived product could reduce pain and lameness, compared to saline in client-owned dogs and human patients with osteoarthritis after one year of treatment (Kon et al., 2018). In a meniscal-tear rat model, the platelet-derived product did not demonstrate clinical improvement, but it did reduce cartilage degeneration (King et al., 2017).

Treatment of tendon and ligament injuries

Tendon and ligament injuries affect animal performance and end the career of a horse or dog hence, it is regarded as a career-limiting disease. Proper early treatment is vital to restore function and structure. The composition of numerous cytokines and growth factors in PRP is predicted to improve clinical outcomes by enhancing tenocyte proliferation (Mazzocca et al., 2012b), collagen and matrix synthesis (Smith et al., 2006; Schnabel et al., 2007), and through influencing vascular density (Bosch et al., 2011). *In vitro* and *in vivo* models have confirmed the anti-inflammatory effects of PRP on tendon inflammation by suppressing the levels of components of the prostaglandin biosynthetic pathway (Zhang et al., 2013).

Muscles injuries

Similar to tendon healing, the use of PRP has shown clinical efficacy in the treatment of muscle injuries through cell proliferation, differentiation, and tissue remodeling after the initial inflammatory response. Previous clinical studies on human patients with muscle injuries have shown a faster recovery and rapid return to play when PRP treatment was carried out simultaneously with rehabilitation in comparison to the rehabilitation alone (Hamid et al., 2014; Reurink et al., 2014).

Fracture and nonunion Management

Among the several strategies for the treatment of bone defects, the most recommended method for filling the small bone defects is to apply bone substitutes or conventional cancellous autologous bone grafting (Hinsche et al., 2003; Calori et al., 2011; Guerado and Fuerstenberg, 2011; Zimmermann and Moghaddam, 2011). Appropriate aligning of the fracture site using internal or external fixators is the main strategy for the management of nonunion fractures. However, novel strategies, such as electromagnetic fields, biodegradable implants, recombinant bone morphogenetic protein 7, and PRP treatment (Akmaz et al., 2004; Calori et al., 2006; Griffin et al., 2011) have been introduced with different outcomes. A meta-analysis found that there is a scarcity of standard randomized clinical trials to investigate the effectiveness of PRP application on the healing rate of nonunion of long bones (Griffin et al., 2012). Several animal

experiments have demonstrated that treatment with PRP in combination with autologous cancellous bone grafting leads to a significant improvement in bone regeneration, in comparison with the isolated application of autologous cancellous bone in long bones of mini-pigs during 6 weeks (Griffin et al., 2011). Considering the above findings, PRP treatment may be promising in overcoming the surgical challenges of the correction of nonunion fractures and improving the current fracture treatments and management by conducting appropriate clinical trials.

Factors affecting the effectiveness of PRP

Although PRP is a promising treatment modality with clear evidence of safety in musculoskeletal medicine, efficacy has been highly dependent on composition and indication. The cellular and molecular content of PRP also depends on the procedure used for preparation (Carmona et al., 2013). The PRP is usually used as an autologous treatment, and product standardization is difficult due to different characteristics and variations among individuals. In horses, inherent factors such as age, breed, and gender affect the whole blood cellular composition, which could potentially influence the effects of PRP (Giraldo et al., 2013), hence clinicians should consider the inherent features of the animal when using platelet-derived products.

The response to PRP as a treatment is affected by PRP composition as well as the condition and type of tissue treated. In many studies on different tissues, lower concentrations of platelets had an insufficient/suboptimal clinical effect, and higher concentrations had inhibitory effects on promoting angiogenesis in cell cultures (Giusti et al., 2009) while leading to apoptosis, downregulation, and desensitization of growth factor receptor, indicating a paradoxical effect on the healing process (Gruber et al., 2002; Haynesworth et al., 2002). Therefore, the selection of intermediate concentrations of platelets might be appropriate for clinical use.

The method used in PRP activation is another factor that should be considered which could have a variable impact on the outcome in this therapy. Platelets can be activated through physical or chemical methods. The different methods of activation are critical factors that should be considered in growth factor concentration (Mazzocca et al., 2012b). Activation of PRP in humans is usually done using thrombin, CaCl₂ (Textor and Tablin, 2012), or with a combination of both (Bendinelli et al., 2010). Some studies suggested the use of CaCl₂ for PRP activation as an effective and inexpensive method that releases more than 80% growth factors (Textor and Tablin, 2012). Other important factors that determine the effectiveness of the PRP treatment are the condition of the tissue before the use of platelet products (acute versus chronic inflammation) as well as the age of the recipient. Better outcomes were reported in younger subjects, in comparison with older patients, and more mild osteoarthritis cases, compared to severe ones (Textor and Tablin, 2012).

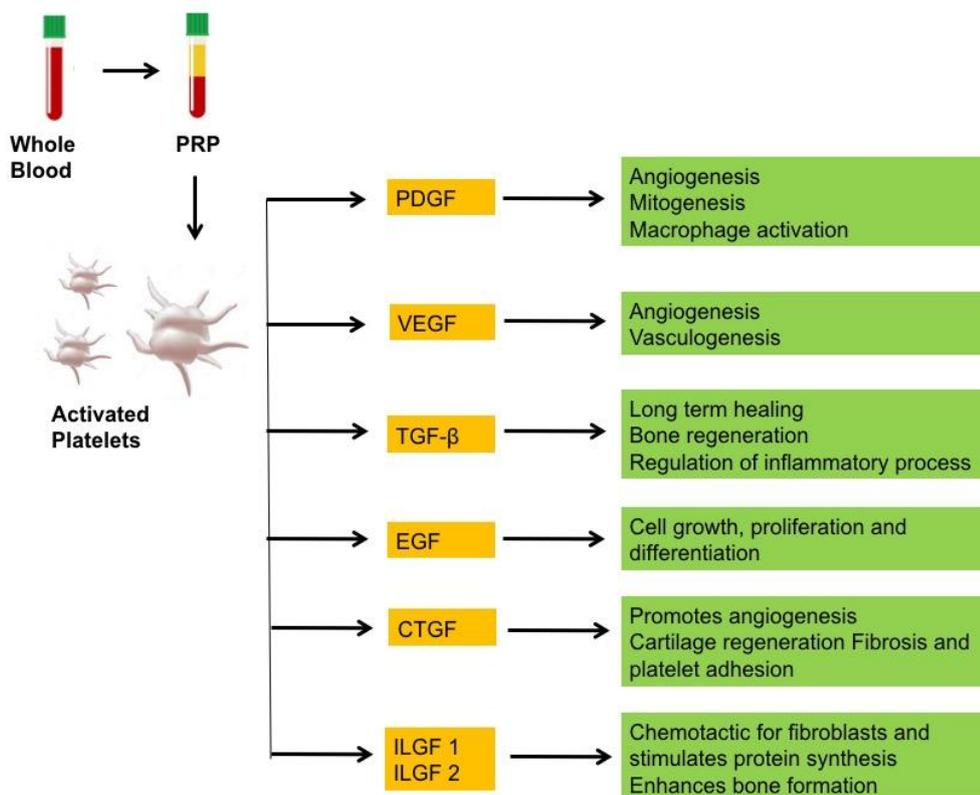


Figure 1. Mechanism of action of PRP. Various growth factors are produced by activated platelets at the site of tissue injury and accelerate the healing and tissue regeneration. PRP: Platelet-rich plasma, PDGF: Platelet derived growth factor, VEGF: Vascular endothelial growth factor, TGF-β: Transforming growth factor beta, EGF: Epidermal growth factor, CTGF: Connective tissue growth factor, ILGF: Insulin like growth factor

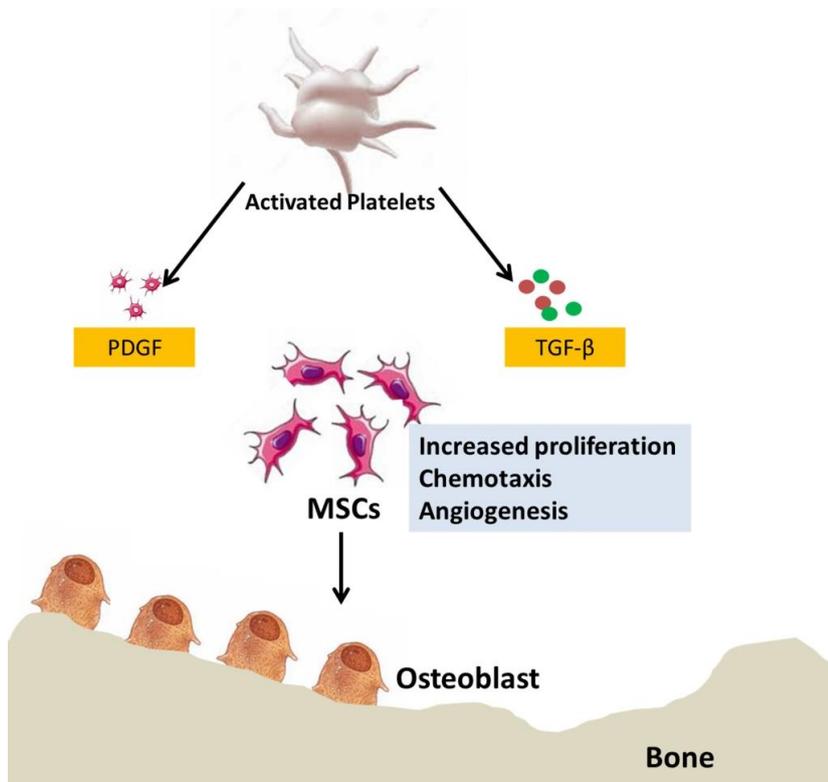


Figure 2. Role of PRP on stem cells in bone and cartilage formation. PRP: Platelet-rich plasma, PDGF: Platelet derived growth factor, TGF- β : Transforming growth factor beta, MSCs: Mesenchymal stem cells

CONCLUSION

It is justifiable for veterinary practitioners to embark on using PRP therapy as a novel modality of treatment for a variety of orthopedic conditions. In response to a growing interest among both patients and surgeons in the use of PRP, recent studies have reported positive outcomes in a variety of conditions. However, due to the paucity of guidelines developed by professional organizations, several important aspects need to be addressed with critical review and rigorous clinical studies. Such efforts would encourage practitioners to formulate a cost-effective, efficacious algorithm for the use of PRP in animals with orthopedic conditions.

DECLARATIONS

Authors' contributions

Both authors participated equally in study design, data collection, and writing. The authors approved the final draft of the manuscript.

Competing interests

The authors declare no conflict of interests.

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