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Platelet-rich plasma, platelet derivatives, and their therapeutic importance in veterinary medicine

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Abstract

Over the past decade, platelet-rich plasma (PRP) and platelet derivatives have been widely investigated in the field of regenerative medicine due to their high concentrations of platelet-related growth factors, cytokines, and other proteins. Recently, many clinical studies have suggested their regenerative therapeutic efficacy in treating several disorders in medical field. However, their therapeutic applications are not well characterized in veterinary medicine as in human and experimental animals. This article reviews functional roles of platelets, scientific concepts, and clinical use of PRP and platelet derivatives in veterinary medicine. It also presents guidelines for veterinary applications of PRP in the future.

Keywords: platelet; platelet-rich plasma; platelet derivatives; growth factors; regeneration

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No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Platelet is the smallest anucleate discoid cell in the bloodstream originating from megakaryocytes in the bone marrow with a diameter of 2 to 4 μm. Canine has a physiological platelet count of 175,000 to 500,000 platelets per microliter of blood. Platelets play a variety of roles in systemic circulation. When a vascular wall is damaged, platelets are activated by exposed collagen and von Willebrand factor from the extracellular matrix that can attract platelets and cause them to roll and adhere [1]. Following activation, platelets change their shape and aggregate as a result of inside-out and outside-in signaling. These aggregates can form primary platelet plug. When they are combined with fibrin, they can form secondary platelet plug [2]. These fibrin networks cover the wound site and eventually achieve hemostasis to stop bleeding [3]. Thus, platelets play a critical role in thrombosis and hemostasis. Likewise, resting platelets consist of various granules including alpha, dense, lysosomal, and glycogen. These granules consist of various growth factors, cytokines, chemokines, and more than 1,500 proteins (including 190 membrane proteins and 262 phosphoproteins) that can be released upon activation of platelets. They are involved in various platelet functional responses [4, 5].

In recent years, platelets have been shown to react to a wide range of signals and regulate a wide variety of biological processes beyond thrombosis and hemostasis due to their granule contents. Platelet and its derivatives have been shown to be able to regulate inflammation, tumor growth

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and metastasis, bacterial defense, wound healing, tissue reorganization, angiogenesis, stem cell migration, and cell proliferation, thus affecting the pathophysiology of various diseases in a paracrine manner [6]. Coagulative and hemostatic functions of platelets are also essential for the early phase of wound healing.

Because of such properties of platelet and its derivatives, technologies have been developed to use platelet-rich plasma (PRP) since early 70s in the field of human medicine, spurring a positive outlook of autologous regenerative medicine [7]. Moreover, the use of PRP preparations has sparked translational research and interest in both scientific and medical communities. Regenerative veterinary medicine is following human progress in a translational trend. The concept of PRP has also recently spread to veterinary medicine. Many veterinarians have suggested the use of PRP for treating several disorders including musculoskeletal injuries, age-related diseases, wound defects, degenerative joint diseases, and skin injuries in equine, canine, feline, and bovine [8]. Despite breakthroughs in our knowledge of platelet function in diverse areas, guidelines or standard protocols for the preparation and use of platelet derivatives are not well characterized yet in veterinary medicine, leading to hurdles for assessing the clinical relevance of platelet-based therapies and for their widespread usage.

This review provides a critical overview of various functional roles of platelet including basic principles, recent advances in technical and scientific concepts underlying the use of PRP, and its derivatives in clinical settings of veterinary medicine.

PLATELETS: MUCH MORE THAN COAGULATION

Upon activation, platelets can secrete proteins and growth factors from their intracellular granules (Table 1) with a pivotal role in wound healing, inflammation cascade, recruitment of WBCs and progenitor cells, modulation of angiogenesis, and other regenerative functions such as cell metabolism, proliferation, differentiation, apoptosis, and vascular remodeling [9, 10]. For example, vascular endothelium growth factor (VEGF), one of platelet angiogenic factors, can promote endothelial cell survival and proliferation, allowing wound to meet their high metabolic requirements and speeding up healing of wounds [11]. Hepatocyte growth factor (HGF), connective tissue growth factor, angiopoietin, and stromal cell-derived factor have angiogenic effects by inducing endothelial cell migration and chemotaxis [12–15]. Additionally, platelet-derived growth factor (PDGF) and fibroblast growth factor in platelets can indirectly increase proliferation of endothelial cells by upregulating the functional activity of VEGF [16, 17]. Moreover, PDGF and transforming growth factor-β1 can act on fibroblasts to replace a transient fibrin scaffold with granulation tissues rich in immature collagens, fibronectin, and proteoglycans [18]. Platelets can also contribute to extracellular matrix reconstruction by secreting matrix metalloproteinases and releasing hydrolases from their lysosomes [19]. Furthermore, quickly after injury, platelets can release large amounts of PDGF and TGF-β. This initial burst can function as a chemoattractant for neutrophils and macrophages, producing inflammation required for early wound healing [20]. HGF and Epidermal growth factor produced by platelets can increase keratinocyte migration, fibroblast activity, and formation

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Table 1. Major platelet granule contents involved in regeneration

Platelet granule contents	Role	Ref
Platelet-derived growth factor (PDGF)	Upregulate VEGF Promote endothelial cell survival and proliferation Reinforce the granulation tissue Produce inflammation in early wound healing	[16, 18, 20]
Vascular endothelium growth factor (VEGF)	Accelerate re-epithelialization and wound closure Granulation tissue formation Promote endothelial cell survival and proliferation	[11, 16, 17]
Fibroblast growth factor (FGF)	Upregulate VEGF Accelerate re-epithelialization	[17]
Transforming growth factor- β1 (TGF-β1)	Reinforce the granulation tissue Produce inflammation in early wound healing	[18, 20]
Matrix metalloproteinase (MMP)	Contribute to debris clearance Reconstruct extracellular matrix	[19]
Epidermal growth factor (EGF)	Accelerate keratinocyte migration, fibroblast and formation of granulation tissue.	[21]
Insulin-like growth factor (IGF)	Stimulate proliferation and migration of fibroblast, osteocyte, chondrocyte, and myocyte	[22, 23]
Hepatocyte growth factor (HGF)	Stimulate epithelial and endothelial cell migration	[12]
Connective tissue growth factor (CTGF)	Promote angiogenesis, cartilage regeneration, fibrosis and platelet adhesion	[15]
Platelet factor 4 (PF4)	Chemoattract monocytes, neutrophils, and fibroblasts into wounds	[24, 25]
Angiopoietin	Chemoattract pericytes	[13]
Stromal cell-derived factor (SCGF)	Chemoattract endothelial precursors	[14]

of granulation of tissue [12, 21]. Insulin-like growth factor can promote the proliferation, survival and differentiation of chondrocytes, osteocytes, myocytes, and fibroblasts which can then improve the recovery of bones and muscles to counter injuries [22, 23]. Platelet factor 4 has chemotactic effects on monocytes, neutrophils, and fibroblasts into the wound, which can promote the inflammatory phase of wound healing [24, 25]. As a result, the release of GFs and cytokines can induce revascularization in injured tissues by endothelial cell proliferation and recovery of ruptured connective tissue via fibroblast deposition.

PLATELET DERIVATIVES AND THEIR USE IN VETERINARY MEDICINE

Because of the aforementioned clinical and biotechnological significance, platelets are currently created and administered with various forms of platelet derivatives. They are used in patients with therapeutic interests. However, these attempts are relatively less in veterinary medicine than in experimental animals or human medicine. Below, we will describe the general knowledge of PRP and platelet derivatives and their use in veterinary medicine.

Platelet-rich plasma

Platelet-rich plasma is an autologous plasma with a higher unactivated platelet concentration above the normal physiology. PRP is typically made by a two-step centrifugation procedure. First, the buffy coat and red blood cell layer are separated from the plasma layer using low-force centrifugation of whole blood obtained with anticoagulants. The obtained plasma layer is

then centrifuged with a high force to separate the platelet pellet from the platelet-poor plasma (PPP). Lastly, PPP is removed and the pellet is resuspended to adjust the PRP concentration. Although PRP can be made with different platelet concentrations depending on the purpose and need, PRP with 3 to 5-fold the number of physiological platelets is commonly recommended for clinical use [26].

Typically, there are two types of PRP: pure-PRP (P-PRP), which solely contains platelets, and leukocyte-PRP (L-PRP), which contains a large number of leukocytes. Thus, the main difference between L-PRP and P-PRP is the potential effect of leukocytes on immune function, proliferation, and differentiation. Several investigations have shown that when L-PRP is used, cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α can lead to inflammation as a side effect [27]. However, some groups have insisted that the PRP requires some leukocyte population to boost the generation of growth factors, release of pain-relieving mediators, and attenuate natural infectious activity [28]. There are still differing perspectives on which is better. More research is needed to optimize leukocyte concentration based on the purpose of treatment.

One of the most important advantages of PRP is that it causes less immunological reactivity. Although hypersensitivity is a side effect when a large amount of non-autologous PRP is administered at a high concentration, multiple studies have shown that: 1) naturally autologous PRP is safe, 2) allogenic PRP is safe from abuse reaction, and 3) even xenogeneic PRP exhibits no significant immunogenicity [29]. Another benefit of PRP is that it is inexpensive, safe, and easy to produce. In general, when PRP is made, around 50% of platelets in whole blood can be recovered. The effective concentration of platelets used for treatment is 3 to 5 times of normal physiological platelets. Thus 6 to 10 mL of whole blood is required to produce 1 mL of PRP. In addition, since 1 mL is used for roughly 100–150 cm^2 for burns and 10 cm^2 for chronic wounds, collecting enough blood from patients for treatment is not an issue except for patients with thrombocytopenia, severe hemorrhage, or hemostatic disorders [30]. Furthermore, it is more cost-effective and easier to prepare than other treatments because it only needs to be centrifuged and resuspended using syringe, blood tube, centrifuge, and complete blood count machine.

However, it is challenging to keep PRP for a long time due to its short lifespan. There is a risk of side effects owing to bacterial proliferation at room temperature. To make up for this, PRP can be stored at 4°C (termed as chilled platelet) or –80°C (termed as cryopreserved platelet). However, such platelets are shown to be ineffective due to their decreased recovery rates. Therefore, PRP must be used within six hours. Extreme care must be taken to avoid microbial contamination when making PRP. In addition, PRP can be easily injected. However, it might be washed away when it is administered to the skin. Therefore, applying graft can be an effective way when using PRP for topical treatment.

PRP is being actively used in veterinary medicine, not just for experimental animals. It was first used as a transfusion for patients with thrombocytopenia and typically has 0.5×10^{11} platelets per unit. PRP transfusion is a very efficient way for thrombocytopenia patients since it provides platelets and plasma itself. In fact, within an hour of its transfusion in dogs with

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thrombocytopenia, platelet counts were shown to be significantly increased and persisted for seven days [31].

In addition to transfusion for treating thrombocytopenia, numerous growth factors listed above enabled the regenerative use of PRP. PRP has been most frequently applied to skin wounds in dogs, including chronic wounds, burning, and infectious wounds [32–34]. Moreover, it is known to be effective in treating musculoskeletal illnesses [35–40]. PRP has been shown to be beneficial for treating diseases like the ones mentioned above in not only dogs but also in horses [41–44], goat [45], and pigs [46].

PRP is not the only hemoderivative with therapeutic significance. PPP is now being targeted for reinvestment in the regenerative industry as a surplus product as it is rich in fibrinogen. Its use has been considered favorable as a sealant for hemostasis because it is inexpensive and accessible [47, 48]. However, PPP has not been used widely in veterinary patients. A study has reported the use of PPP in bone repair of canine [47]. Likewise, frozen plasma can also be used as a fibrin sealant as it can be prepared semi-rigid to elastic that can act as a biological tissue glue through which cells can migrate [49]. Frozen plasma has been used for veterinary surgical purposes in ophthalmology, orthopedics, and reconstructive surgery [50].

Despite the huge demand for PRP and PPP, there is a confusion in the interpretation of scientific outcomes concerning their real therapeutic effects.

Platelet gel (PG)

For more effective treatment, several platelet derivatives have been created to overcome the limitation of PRP. PG is commonly made by combining PRP with thrombin, calcium gluconate, or calcium chloride, resulting in gelation of the platelet concentrate [51]. PG is more ideal for topical treatment in skin since it is solid, as opposed to PRP. In addition, it has the advantage of being able to be applied for a longer period of time than PRP because GFs are secreted more gradually in PG. PG can also accelerate the healing of chronic wounds in dogs [52]. In some human medical research studies, PG is more effective than PRP because its three-dimensional fibrin matrix allows platelets to adhere to the fibrin scaffold with a sustained release of growth factors [53]. However, depending on the strength of the gel, injection might be challenging. Proper treatment might also be problematic because how much regenerative growth factor is present in the gel is not known.

Platelet-rich fibrin (PRF)

PRF is blood clot that is prepared by immediately centrifuging whole blood without using an anticoagulant. Centrifugation causes the coagulation cascade to be activated and the production of thrombin rapidly, which leads to the generation of fibrin clot and the activation of platelets [54]. The PRF produced in this way is called leukocyte-PRF (L-PRF). It has a number of advantages, including being easier to make than PRP, being longer-lasting, and not requiring gelation additives like PG. PRF membranes can release a high quantity of GFs for a prolonged period (up to 2 weeks), acting as a space filler due to their scaffold-like function and GF temporal release [55, 56]. PRF is mostly used for oral and dental treatment and healing. It

has been reported that PRF has a similar therapeutic effect on furration perception to PRP in dogs [57]. PRF might be one of the most versatile and accessible platelet derivatives available for veterinary regenerative therapy, with potential usage in a variety of clinical settings. However, in the case of PRF, its concentration in platelets is lower than that in other tives since it is not concentrated. Thus, its therapeutic efficacy might be limited. In addition, how much growth factors are present in PRF is unknown. Potential inflammatory processes may arise in locations where leukocytes are concentrated due to centrifugation [58]. To compensate for the potential risk of inflammation in L-PRF, advanced-PRF (A-PRF) has been developed, which can distribute leukocytes equally using low-speed centrifugation. Some studies have reported that A-PRF is more effective than L-PRF [59].

Platelet lysate (PL)

PL is a growth factor-rich cell-free supernatant generated by disrupting platelets in PRP by two to three freeze/thaw cycles [60]. During production, platelets are lysed in an easily standardized protocol that can release GFs, cytokines, and other associated proteins. This process can reduce batch-to-batch variation. Since it aids in cell growth and proliferation, it has typically been known as a viable alternative to fetal bovine serum. Although it is not commonly utilized for regeneration, PL also has regenerative effect in veterinary medicine [61]. PL has a high potential to overcome issues related to allogeneic administration and immunogenic reactions of other blood-derived products. However, currently there are only a few cases where PL has been applied to veterinary clinics.

Lyophilized platelet-rich plasma (PRP)

Lyophilized PRP is frozen PRP, after water sublimation and vapor elimination. Lyophilized PRP has been proven to be beneficial in an acute wound healing model as PRP [62]. However, it is rarely applied in veterinary clinics. Although lyophilized PRP has the limitation of requiring special equipment for freeze-drying, as it is typically in powder form, it is one of the platelet derivatives that is receiving attention because it can be simply applied by being dissolved in distilled water. In addition, it can be stored stably for a long time at room temperature. Thus, it can be easily commercialized.

Overall, until now, new platelet derivatives have been developed to overcome the limitations of PRP and conventional platelet derivatives. In the case of PRF, lyophilized PRF has been developed by combining lyophilization to overcome the limitation of lifespan [63]. Furthermore, PRP is used as a PRP-hydrogel by grafting hydrogel, a biocompatible material that is good for wound space filling [64]. These endless efforts will aid in the development of more efficient platelet derivatives. Many veterinary applications of new platelet derivatives will contribute to animal health and, ultimately, human health.

CONCLUDING REMARKS AND FUTURE DIRECTION

We reviewed the use of PRP and platelet derivatives in veterinary medicine. The majority of

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drugs used to treat wounds nowadays are not natural drugs. Thus, there might have some adverse effects. However, since PRP is acquired from animal itself, there are no negative effects. Thus, it can be used alone or in combination with other wound-healing compounds to increase efficiency. However, it is still not established what platelet concentration is the best based on the site and severity of injury. Studies comparing efficacies of PRP and platelet derivatives are relatively lacking in veterinary fields. Additionally, there are a considerable number of cases of applying PRP and platelet derivatives in experimental animals, although such cases are far less in veterinary clinics. More veterinary applications of PRP and platelet derivatives will be extremely beneficial to boost animal health and human health through translational medicine in the future.

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