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Mini Review

Therapeutic Potential of Platelet-Rich Plasma in Canine Medicine

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Abstract

Platelets are the reservoir of growth factors and play a major role in several physiological processes, such as coagulation, angiogenesis, immune response, and tissue repair. Platelet concentrates are broadly classified into two groups depending on their fibrin content, namely platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). They are further divided based on their leucocyte contents. The PRP is plasma containing supra-physiological concentrations of the platelets. The growth factors present in the PRP play a crucial role in the promotion of local angiogenesis, regulation of cellular activity, stem cell homing, proliferation and differentiation of different stem cells, and deposition of matrix proteins contributing to tissue regeneration. This review aimed to establish the therapeutic potential of PRP in canine medicine with a particular focus on the applications in ophthalmology, dermatology, and musculoskeletal disorders. A systematic literature review was performed to identify the literature published during the past 20 years (2001-2021) using authentic academic databases, such as PubMed, Science Direct, Google Scholar, and Scopus. In the initial search, 556 articles were identified and based on the specific inclusion and exclusion criteria, 59 articles were selected for further analysis. The clinical efficacy of PRP depends on the number of platelets and the growth factor concentration. The PRP-based biological therapy has broad clinical applications in musculoskeletal pathologies. It is a simple, safe, and cost-effective method that can be used to treat various diseases and disorders in canine practice. For example, PRP is used for managing corneal ulcers, corneal erosion, alkali burn, keratoconjunctivitis sicca, burn wounds, chronic wounds, cutaneous ulcers, acute traumatic bone fractures, tendinopathies, cartilage pathologies, osteoarthritis, and abdominal wall defects either as monotherapy or as an adjunctive therapeutic agent. In addition, PRP is widely used as a carrier of mesenchymal stem cells for transplanting into bone defects. Therefore, allogeneic PRP therapy can be considered a simple, safe, and cost-effective method for the treatment of various diseases and disorders in canine practice. The therapeutic application of PRP in canine medicine is limited in the present study due to the lack of consensus for collection, characterization, and clinical use. Hence, further studies are required to establish the actual worth of PRP-based regenerative strategies in canine medicine.

Keywords: Canine medicine, Canine practice, Dermatology, Platelet-rich plasma, Regenerative medicine

1. Context

Platelet-rich plasma (PRP) is a biological product containing a supra-physiological concentration of platelets (1, 2). In other words, PRP is plasma with a platelet count higher than peripheral blood. It is derived from the whole blood after undergoing centrifugation (2, 3). The platelet contains three types of granules (alpha, delta, and lambda) that store several growth factors and proteins. Alpha-granules are the most abundant granules present within the platelets (4). In addition to growth factors, platelets deliver chemokines that help to recruit white blood cells (5). Furthermore,

the macromolecules, such as fibrinogen and fibronectin, assist in the healing process (6).

The PRP is rich in several important growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta1 (TGF-β1), epidermal growth factor (EGF), basic fibroblast growth factor (b-FGF), and hepatocyte growth factor (HGF) that contributes to their biological activity and therapeutic potential (3). These growth factors play a crucial role in the promotion of local angiogenesis, regulation of cellular activity, stem cell homing, proliferation and differentiation of different stem cells, and deposition of matrix proteins contributing to tissue regeneration (1, 3, 7). Therefore, PRP has received wide acceptance in regenerative medicine and is currently being used for bone, cartilage, and tendon repair (7).

The PRP can be prepared by different methods, such as gravitational centrifugation techniques, autologous selective filtration technology (plateletpheresis), and standard cell separators (1, 8). Among these, gravitational centrifugation techniques utilizing laboratory centrifuges are commonly used for PRP preparation. The qualitative characteristics of the PRP changes depending on the cellular composition (9, 10). However, the composition of PRP is, in turn, dependent on the centrifugal force and duration (10). The variables that could affect the PRP characteristics are broadly classified into two groups, namely PRP preparation factors and patient/donor factors. Factors, such as the age, gender, and physiological status of the patient could affect not only the PRP characteristics but also the therapeutic outcome (11). In addition, the PRP preparation factors, such as the method of activation, type of anticoagulant, centrifugal force (g) and duration, and operator skill also affect the qualitative and quantitative characteristics of PRP (10, 11).

2. Evidence Acquisition

This review aimed to establish the therapeutic potential of PRP in canine medicine with a particular focus on the applications in ophthalmology, dermatology, and musculoskeletal disorders. A systematic literature review was performed to identify literature during the past 20 years (2001-2021) using authentic academic databases, such as PubMed, Science Direct, Google Scholar, and Scopus. The search keywords included platelet-rich plasma, canine, dog, canine medicine, classification, platelet concentrates, ophthalmology, dermatology, and musculoskeletal disorders. The following inclusion criteria were used for literature selection: availability of information on classification, composition, properties, and therapeutic potential of PRP with a specific focus on canine medicine. The articles written in languages other than English were not included in this review.x

3. Results

In the initial search, 556 articles were identified. It should be mentioned that relevant, critical, and most recent literature mainly belonging to the past five years (2016-2021) were given preference. Based on the specific inclusion and exclusion criteria, 59 articles were selected for further analysis. After the literature assortment, the obtained data were used for developing this review.

3.1. Classification of Platelet-Rich Plasma

Platelet concentrates are broadly classified into two groups depending on their fibrin content, namely PRP and platelet-rich fibrin (PRF). Each of these categories is further divided based on leucocyte content: pure platelet-rich plasma (P-PRP), pure platelet-rich fibrin (P-PRF), leucocyte- and platelet-rich plasma (L-PRP), leucocyte- and platelet-rich fibrin (L-PRF) (12). Several PRP classification systems have been developed in the past decade; nevertheless, the Dohan Ehrenfest classification is the most widely used due to its ease of use (13).

Recently, the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (PPS-ISTH) developed an updated classification system for platelet concentrate that considers red blood cell (RBC) concentration (1). According to PPS-ISTH

classification, platelet concentrates are classified into PRF, L-PRF, RBC-rich platelet-rich fibrin, RBC-rich, and leukocyte-rich platelet-rich fibrin, PRP, L-PRP, RBC-rich PRP, and RBC-rich and leukocyte-rich PRP (1). Several classification systems are currently available; however, most of them failed to define the variables that affect the biological properties of PRP (9).

The commercially available PRP-production systems differ in the preparation method, quantity of blood processed, and the yield of PRP produced. The final PRP product also varies in platelet, leukocyte, and red blood cell concentrations (14, 15). Therefore, the PRP used in every study should be characterized before their therapeutic evaluation. In addition, researchers studying the clinical efficacy of PRP should strictly adhere to the minimum reporting requirements (9, 16-18). To improve the reproducibility of the studies evaluating PRP, the researchers should define all the variables that could affect the efficacy of PRP (19). This will also enable the comparison of similar *in vitro*, *in vivo*, and clinical studies to establish a standard therapeutic protocol for future studies.

3.2. Growth Factors in Platelet-Rich Plasma

Platelets are the reservoir of growth factors and play a major role in several physiological processes, such as coagulation, angiogenesis, immune response, and tissue repair. The growth factors present in the PRP are released mainly from the alpha granules of activated platelets (20, 21). These growth factors have the potential to accelerate mesenchymal stem cell differentiation as well as fibroblasts and osteoblasts proliferation (10). The clinical efficacy of PRP depends on the number of platelets and the growth factor concentration (20). The growth factors and cytokines present in the PRP are produced from different cellular sources (see Table 1) (22).

Table 1. Growth factors and cytokines present in platelet-rich plasma and their cellular source. Modified from Everts et al. (2020) (22).

Growth factors and cytokines*	Cell sources
PDGF (AA-BB-AB)	Platelets, endothelial cells, macrophages, smooth muscle cells
TGF (α–β)	Macrophages, T lymphocytes, keratinocytes
VEGF	Platelets, macrophages, keratinocytes, endothelial cells
EGF	Platelets, macrophages, monocytes
(a-b)-FGF	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts
CTGF	Platelets, fibroblasts
IGF-1	Platelets, plasma, epithelial cells, endothelial cells, fibroblasts, osteoblasts, bone matrix
HGF	Platelets, mesenchymal cells
KGF	Fibroblasts, mesenchymal cells
Ang-1	Platelets, neutrophils
PF4	Platelets
SDF-1α	Platelets, endothelial cells, fibroblasts
TNF	Macrophages, mast cells, T lymphocytes

*__Abbreviations__: Ang-1: angiopoietin-1; CTCG: connective tissue growth factor; EGF: epidermal growth factor; FGF: fibroblast growth factor; HGF: hepatocyte growth factor; IGF: insulin-like growth factor; KGF: keratinocyte growth factor; PDGF: platelet-derived growth factors; PF4: platelet factor 4; SDF: stromal cell-derived factor; TGF: transforming growth factor; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor.

During haemostasis, the platelet is activated *in vivo* with the help of thrombin (23). This is followed by the release of growth factors present within the alpha granules. Once the PRP is produced, it can be activated by adding calcium chloride or thrombin (22). In addition to growth factors, the alpha granules of platelets contain adhesive proteins (e.g., fibrinogen, laminin-8, thrombospondin-1, and thrombospondin-2), chemokines (e.g., CCL5, CCL3, CCL-2), integral membrane proteins (GPIba-IX-V, GPVI, aIIb3, p-selectin, TLT-1), immune mediators (e.g., factor D, factor H, complement C3 precursor, and complement C4 precursor), clotting factors and their inhibitors (e.g., antithrombin, factor V, factor IX, factor S, and tissue factor pathway inhibitor) (4).

3.3. Platelet-Rich Plasma in Ophthalmology

The cornea has three functions; accordingly, it filters the UV light, acts as aphysical barrier, and helps in refraction (24). The cornea consists of three layers, and affection of any of these layers, with deficiency of limbal stem cells, dystrophy of the cornea, and bullous keratopathy, can cause visual obtuseness (25). Several factors are required to facilitate the wound healing process, like growth factors, glucose, and vitamins found abundantly in the blood (26). Three forms of PRP therapy can be applied to the ocular surface:

1. Drop Form: The ocular surface is treated using topical autologous PRP drops (27).

2. Injectable Form: The PRP is injected via the subconjunctival or intrastromal route (28, 29).

3. Clot Form: Platelet-rich clot is used to make sure that the platelets and growth factors are retained. Afterward, the eye is covered with the third eyelid (30).

The PRP can be used as a therapeutic agent in keratitis ulcers, corneal erosion, and other corneal injuries (31). Drop and clot form of PRP is proven to be a new advancement in regenerative medicine for corneal ulcer therapy in canines (29). The PRP drops were found to promote the healing process of moderate or grade II corneal ulcers in dogs and prevent their advancement to aggressive forms of ulcers (32). Autologous PRP is reported to be effective in dogs suffering from moderate keratoconjunctivitis sicca (31). In addition, PRP could be used for the management of inflammatory or traumatic conditions of the anterior ocular surface (31, 33). Subconjunctival injection of autologous PRP is effective in treating corneal ulcers in dogs. However, the number of injections depends on the type of corneal ulcer (29).

Autologous PRP is also used as adjunctive therapy along with diamond-burr debridement for managing spontaneous chronic corneal epithelial defects in canines (33). The combination of intrastromal PRP and oral doxycycline therapy was found effective in managing ocular emergencies, such as corneal chemical burns (alkali burn) (28). Due to the protective activity, PRP can be routinely used after surgical interventions on the cornea as supportive therapy (31). The use of autologous PRP in canine practice has several advantages as it is a safe and cheap method that is easy to perform in any clinical setting (29).

3.4. Platelet-Rich Plasma in Dermatology

Loss of skin integrity is called a wound, and once it is formed, the physiological process known as wound healing is initiated (34). The PRP has an interactive biological effect on the healing process due to concentrated growth factors that have a synergistic impact in the clinical arena where there is demand for rapid healing and regeneration of tissues. PRP is also responsible for the recruitment of mesenchymal cells and the synthesis of extracellular matrix (35). The healing effects of PRP are mediated by PDGF, TGFβ, VEGF, FGF, EGF, IGF, IL-8, and TNFα. These factors have various functions, such as enhancement of re-epithelialization, collagen synthesis, and angiogenesis (36). Autologous PRP was found to be beneficial to the treatment of large cutaneous defects. They can also be used for accelerating delayed wound healing (37). Furthermore, L-PRP exhibits antibacterial activity due to the high concentration of leucocytes and, therefore, can be considered ideal for managing chronic wounds and cutaneous ulcers (38). In addition, allogenic topical PRP is also effective in the management of cutaneous soft-tissue wounds in canine practice (39).

Iacopetti (2020) recommended topical administration of autologous PRP and its repetition after two weeks, considering that the half-life of platelets in dogs is approximately 10 days (40). The second application will act as a good catalyst for re-epithelialization and wound contraction. The protocol involves the injection of 0.5 ml PRP into the wound with a 26G needle via the intradermal route into the lesion to hasten the healing process (41). The major advantage of PRP therapy is the absence of abnormal tissue formation or keloid/pathologic scarring (42). Furthermore, the hair fully re-grows on the affected area of the bodies of the dogs after therapy (39). Therefore, in the case of large subacute wounds, PRP is an excellent alternative therapy that is cost-effective and easy to perform. In addition, PRP is ideal for managing burn wounds in dogs. The use of autologous PRP in full-thickness burn wounds was associated with accelerated wound healing and reduced healing time (43). In addition, PRP reduced secondary complications due to the burn wound (43).

3.5. Platelet-Rich Plasma in Musculoskeletal Disorders

The PRP has established clinical utility in fracture management since it can accelerate bone healing (44, 45). Therefore, PRP is currently being evaluated for the management of non-union fractures (45). The combined use of PRP and stem cells will enhance vasculogenesis in the newly formed bone tissue, accelerating the process of healing (46, 47). The PRP can also be used in combination with external skeletal fixation methods for managing acute traumatic bone fractures in canines (44).

In this study, the application of PRP at the fracture site resulted in increased swelling and oedema during the initial postoperative days due to the activation of angiogenesis. Enhanced angiogenesis led to heat, pain, and redness in the area surrounding the fracture (44, 48). The PRP was found to assist the process of bone healing when used in combination with adipose tissue-derived mesenchymal stem cells seeded biphasic calcium phosphates bioceramic (HA/TCP) granules for managing canine alveolar surgical bone defects (46). *In vitro* studies have confirmed that the addition of PRP can enhance the mineralization and proliferation capacity of adipose tissue-derived mesenchymal stem cells incubated with HA/TCP granules (47). The combined use of bone marrow-derived mesenchymal stem cells and PRP accelerated the distraction osteogenesis (increased distraction rate) using the Ilizarov fixator in canines (49).

According to the available literature, L-PRP is more beneficial in tendinopathies, whereas P-PRP is ideal for cartilage pathology (2). Similarly, L-PRP is commonly used for managing soft tissue injuries (5). The L-PRP is also used for managing several musculoskeletal disorders, such as bursitis, tendinitis, tendon/ligament rupture, osteoarthritis, osteochondral dissecans, joint laxity, lumbosacral stenosis, and patellar luxation (5, 50). It is also used post-surgically after performing femoral head osteotomy and tibial plateau levelling osteotomy as supportive therapy (5). In addition, PRP is widely used as a carrier of mesenchymal stem cells for transplanting into bone defects. The gel form is also used as a scaffold for bone formation (49, 51).

In vivo studies have confirmed that treatment with PRP (pre-treatment or simultaneous administration) can ameliorate lidocaine-induced cytotoxicity in canine chondrocytes (52). Therefore, PRP can be used as a protective treatment in canines receiving intra-articular lidocaine injection. Single-dose administration of allogeneic PRP has been reported to be safe and effective in managing canine osteoarthritis. The PRP was administered into the intra-articular cavity after echo-guided localization of the cavity (50). Intra-articular injection of PRP improved limb function and decreased pain in the canine anterior cruciate ligament model of osteoarthritis (53). In addition, intra-articular injections of hyaluronic acid in combination with PRP were found to be effective for the short-term

management of canine osteoarthritis symptoms (6).

Furthermore, the combination of hyaluronic acid and PRP yielded better cartilage preservation than monotherapy using hyaluronic acid. The aim of PRP therapy in canine osteoarthritis is to deliver a large concentration of growth factors and bioactive proteins produced by platelets to the joint cavity (6). The PRP can also be used as a therapeutic agent for managing chronic lameness in dogs with stifle degenerative joint disease secondary to cranial cruciate ligament rupture (Figure 1) (54). The PRP also promotes graft maturation during anterior cruciate ligament reconstruction due to its ability to enhance revascularization and reinnervation (55).

3.6. Miscellaneous Applications

The PRP can be used as an adjunct therapeutic strategy for managing abdominal wall defects in veterinary practice (56). The addition of allogeneic PRP to the polyester/cotton fabric used for correcting abdominal wall defect increased tissue deposition and neovessel formation. In addition, the recurrence rate and the incidence of postoperative peritoneal adhesions were reduced (56). Besides, the ability of PRP to stimulate tissue regeneration can be utilized to induce regenerated periodontal tissues. The combined use of PRP and adipose tissue-derived stem cells promote periodontal tissue regeneration in canines (57). The PRP can also be used as an adjunct therapeutic strategy for improving the success rate of revascularization procedures in dogs which is performed for the management of immature dog teeth (58).

3.7. Limitations

The therapeutic application of PRP in canine medicine was limited in the present study due to the lack of consensus for collection, characterization, and clinical use. In addition, improper reporting of clinical trials and case studies evaluating PRP further limited our ability to compare the therapeutic efficacy based on the available data (16-18). Advanced characterization techniques (growth factor estimation) are required to identify the specific component present in PRP (growth factors) that contributed to a particular therapeutic effect (59). Therefore, further studies should focus on identifying the growth factors that contribute to the therapeutic potential of PRP in different clinical applications.

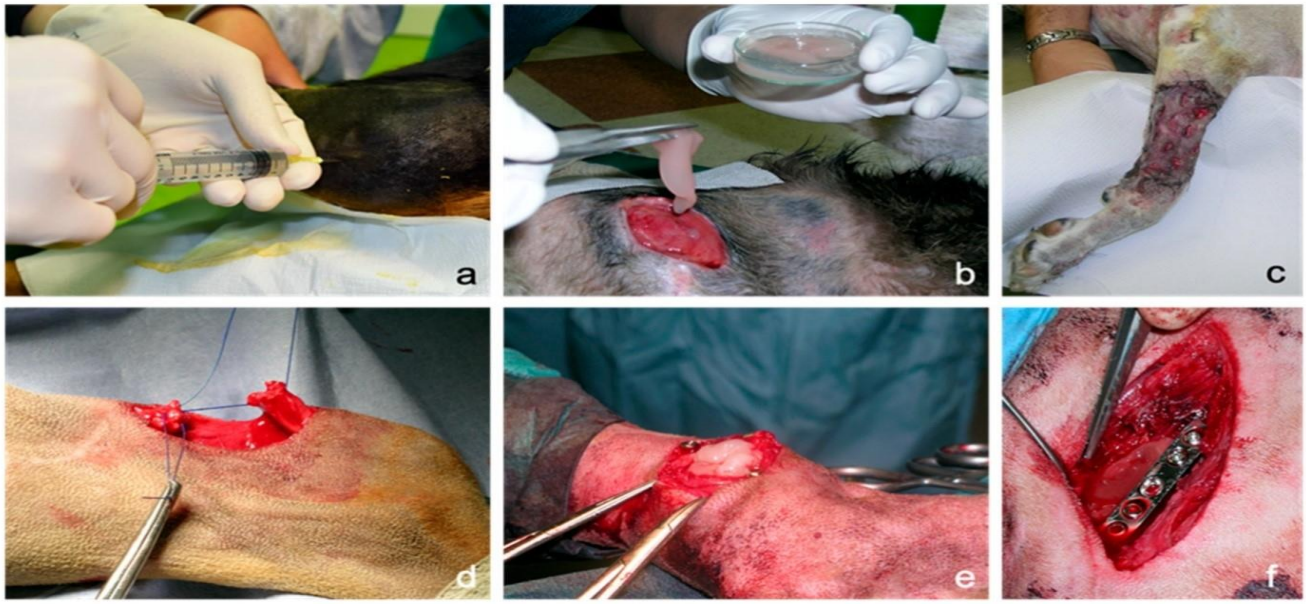

Figure 1. Therapeutic applications of platelet-rich plasma (PRP) in canine practice: **(a)** Intra-articular injection for managing stifle joint osteoarthritis. **(b)** Topical PRP therapy using gel formulation in a chronic wound over the point of the shoulder. **(c)** PRP for managing traumatic forelimb wound. It is used along with free mesh skin autograft for wound bed preparation and engraftment stimulation. **(d)** PRP is used as biological augmentation for managing acute calcaneal tendon rupture after performing the surgical repair by end-to-end suture. **(e)** PRP is used as an alternative to the cancellous bone during arthrodesis of a metatarsophalangeal joint. **(f)** Application of PRP during the surgical treatment of a non-union femoral fracture. Reproduced from Perinelli et al. (2020) (21) under the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

4. Conclusions

Allogeneic PRP therapy can be considered a simple, safe, and cost-effective method to treat various diseases and disorders in canine practice. However, there is a need for conducting an evidence-based assessment of different PRP preparations to identify their specific applications. This will help to establish the PRP type that is suitable for each clinical indication. The PRP-based biological therapy has broad clinical applications in musculoskeletal pathologies. It is a simple, safe, and cost-effective method that can be used to treat various canine diseases and disorders. For example, PRP is used for managing corneal ulcers, corneal erosion, alkali burn, keratoconjunctivitis sicca, burn wounds, chronic wounds, cutaneous ulcers, acute traumatic bone fractures, tendinopathies, cartilage pathologies, osteoarthritis, and abdominal wall defects either as monotherapy or as an adjunctive therapeutic agent. In addition, PRP is widely used as a carrier of mesenchymal stem cells for transplanting into bone defects.

In addition to the established double centrifugation protocols, several commercial PRP preparation kits are now available in the market that can be used to produce PRP with varying cellular compositions. Therefore, it is necessary to follow the most recent PRP classification and coding system while defining the final product (59). In addition, future studies that evaluate the therapeutic potential of PRP should strictly adhere to the minimum reporting requirements put forward by the competing authority while describing the characteristics of PRP and its production method. This will ensure repeatability and ensure easy comparison of similar studies.

Authors' Contribution

Study concept and design: K. S.
Acquisition of data: K. S. and K. J.
Analysis and interpretation of data: K. S. and K. J.
Drafting of the manuscript: K. S., K. J. and K. D.
Critical revision of the manuscript for important intellectual content: K. D., R. K., A. M. P., and A.
Administrative, technical, and material support: K. D., R. K., A. M. P. and Amarpal

Conflict of Interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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References

1. Harrison P; Subcommittee on Platelet Physiology. The use of platelets in regenerative medicine and proposal for a new classification system: guidance from the SSC of the ISTH. J Thromb Haemost. 2018;6(9):1895-1900.
2. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review. EFORT Open Rev. 2021;6(4):225-235.
3. Kaushik A, Kumaran MS. Platelet-Rich Plasma: The Journey so Far! Indian Dermatol Online J. 2020;11(5):685-692.
4. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet Rich Plasma: a short overview of certain bioactive components. Open Med (Wars). 2016;11(1):242-247.
5. King W, Cawood K, Bookmiller M. The Use of Autologous Protein Solution (Pro-Stride®) and Leukocyte-Rich Platelet-Rich Plasma (Restigen®) in Canine Medicine. Vet Med (Auckl). 2021;12:53-65.
6. Lee MI, Kim JH, Kwak HH, Woo HM, Han JH, Yayon A, et al. A placebo-controlled study comparing the efficacy of intra-articular injections of hyaluronic acid and a novel hyaluronic acid-platelet-rich plasma conjugate in a

canine model of osteoarthritis. J Orthop Surg Res. 2019;14(1):314.
7. Qian Y, Han Q, Chen W, Song J, Zhao X, Ouyang Y, et al. Platelet-Rich Plasma Derived Growth Factors Contribute to Stem Cell Differentiation in Musculoskeletal Regeneration. Front Chem. 2017;5:89.
8. Sharun K, Pawde AM, Pal A. Platelet-rich plasma (PRP) for skin graft enrichment: The need for a universal PRP classification system. Int Wound J. 2020;17(6):2038-2039.
9. Sharun K, Pawde AM. Platelet-rich plasma (PRP) for post-traumatic osteoarthritis: classification and coding systems. Osteoarthritis Cartilage. 2020;28(12):1581-1582.
10. Cao Y, Zhu X, Zhou R, He Y, Wu Z, Chen Y. A narrative review of the research progress and clinical application of platelet-rich plasma. Ann Palliat Med. 2021;10(4):4823-4829.
11. Sharun K, Pawde AM. Variables affecting the potential efficacy of platelet-rich plasma in dermatology. J Am Acad Dermatol. 2021;84(1):e47-e48.
12. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158-67.
13. Sharun K, Pawde AM, Amarpal. Classification and coding systems for platelet-rich plasma (PRP): a peek into the history. Expert Opin BiolTher. 2021;21(2):121-123.
14. Franklin SP, Garner BC, Cook JL. Characteristics of canine platelet-rich plasma prepared with five commercially available systems. Am J Vet Res. 2015;76(9):822-7.
15. Carr BJ, Canapp SO Jr, Mason DR, Cox C, Hess T. Canine Platelet-Rich Plasma Systems: A Prospective Analysis. Front Vet Sci. 2016;2:73.
16. Sharun K, Pawde AM. In vitro studies using platelet-rich plasma: Minimum reporting requirements. Cell Biol Int. 2020;44(12):2380-2382.
17. Sharun K, Pawde AM. Platelet-Rich Plasma for Burn Wound: Minimum Reporting Requirements. J Burn Care Res. 2020;41(6):1309.
18. Sharun K, Pawde AM. Minimum requirements for reporting clinical trials evaluating the therapeutic potential of platelet-rich plasma. J Am Acad Dermatol. 2021;84(1):e43-e44.
19. Sharun K, Pawde AM. Platelet-rich plasma for hip osteoarthritis: comparing the variables in production protocol and composition. Clin Rheumatol. 2020;39(12):3899-3901.
20. Lubkowska A, Dolegowska B, Banfi G. Growth factor content in PRP and their applicability in medicine. J BiolRegulHomeost Agents. 2012;26(2 Suppl 1):3S-22S.
21. Perinelli DR, Bonacucina G, Pucciarelli S, Cespi M, Serri E, Polzonetti V, et al. Rheological Properties and Growth Factors Content of Platelet-Rich Plasma: Relevance in Veterinary Biomedical Treatments. Biomedicines. 2020;8(10):429.
22. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. Int J Mol Sci. 2020;21(20):7794.
23. Gentile P, Cole JP, Cole MA, Garcovich S, Bielli A, Scioli MG, et al. Evaluation of Not-Activated and Activated PRP in Hair Loss Treatment: Role of Growth Factor and Cytokine Concentrations Obtained by Different Collection Systems. Int J Mol Sci. 2017;18(2):408.
24. Wilson SA, Last A. Management of corneal abrasions. Am Fam Physician.;70(1):123-8.
25. Oie Y, Nishida K. Regenerative medicine for the cornea. Biomed Res Int. 2013;2013:428247.
26. Tanidir ST, Yuksel N, Altintas O, Yildiz DK, Sener E, Caglar Y. The effect of subconjunctival platelet-rich plasma on corneal epithelial wound healing. Cornea. 2010;29(6):664-9.
27. Alio JL, Rodriguez AE, Abdelghany AA, Oliveira RF. Autologous Platelet-Rich Plasma Eye Drops for the Treatment of Post-LASIK Chronic Ocular Surface Syndrome. J Ophthalmol. 2017;2017:2457620.
28. Charalambidou G, Kofidou E, Papaioannou N, Karampatakis V, Komnenou, A. The effect of intrastromal PRP and oral doxycycline in corneal wound healing after alkali burn. J Hellenic Vet Med Soc. 2019;69(4):1213-1226.
29. Farghali HA, AbdElKader NA, AbuBakr HO, Ramadan ES, Khattab MS, Salem NY, et al. Corneal Ulcer in Dogs and Cats: Novel Clinical Application of Regenerative Therapy Using Subconjunctival Injection of Autologous Platelet-Rich Plasma. Front Vet Sci. 2021;8:641265.
30. Merlini NB, Fonzar JF, Perches CS, Sereno MG, Souza VL, Estanislau CA, et al. Use of platelet rich plasma on corneal ulcers in dogs. Arq Bras Med Vet Zootec. 2014;66(6):1742-1750.
31. Vatnikov YA, Erin IS, Suleimanov SM, Kulikov EV, Seleznev SB, Lutsay VI, et al. Effect of Autologous Plasma Treatment on the Cornea Regeneration with

Keratoconjunctivitis Sicca in Dogs. J Anim Health Prod. 2020;8(1): 1-7.

32. Mishra A, Shahi A, Das B, Jawre S, Singh R, Nayak A. Evaluation of PRP drop and L-PRF Membrane for Aggressive Ulcerative Keratitis in Dogs. J Anim Res. 2021;11(1):181-185.
33. Edelmann ML, Mohammed HO, Wakshlag JJ, Ledbetter EC. Clinical trial of adjunctive autologous platelet-rich plasma treatment following diamond-burr debridement for spontaneous chronic corneal epithelial defects in dogs. J Am Vet Med Assoc. 2018;253(8):1012-1021.
34. Sardari K, Reza Emami M, Kazemi H, Reza Movasagi A, AfkhamiGoli A, Lotfi A, et al. Effects of platelet-rich plasma (PRP) on cutaneous regeneration and wound healing in dogs treated with dexamethasone. Comp Clin Pathol. 2010;20(2):155–162.
35. Yuan T, Zhang CQ, Tang MJ, Guo SC, Zeng BF. Autologous Platelet-rich Plasma Enhances Healing of Chronic Wounds. Wounds. 2009;21(10):280-5.
36. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J Bone Joint Surg Br. 2009;91(8):987-96.
37. Kim JH, Park C, Park HM. Curative effect of autologous platelet-rich plasma on a large cutaneous lesion in a dog. Vet Dermatol. 2009;20(2):123-6.
38. Crovetti G, Martinelli G, Issi M, Barone M, Guizzardi M, Campanati B, et al. Platelet gel for healing cutaneous chronic wounds. TransfusApher Sci. 2004;30(2):145-51.
39. Chung TH, Baek DS, Kim N, Park JH, Park C. Topical allogeneic platelet-rich plasma treatment for a massive cutaneous lesion induced by disseminated intravascular coagulation in a toy breed dog. Ir Vet J. 2015;68(1):4.
40. Iacopetti I, Patruno M, Melotti L, Martinello T, Bedin S, Badon T, et al. Autologous Platelet-Rich Plasma Enhances the Healing of Large Cutaneous Wounds in Dogs. Front Vet Sci. 2020;7:575449.
41. Jee CH, Eom NY, Jang HM, Jung HW, Choi ES, Won JH, et al. Effect of autologous platelet-rich plasma application on cutaneous wound healing in dogs. J Vet Sci. 2016;17(1):79-87.
42. Tambella AM, Attili AR, Dini F, Palumbo Piccionello A, Vullo C, Serri E, et al. Autologous Platelet Gel to Treat Chronic Decubital Ulcers: A Randomized, Blind Controlled Clinical Trial in Dogs. Vet Surg. 2014;43: 726-733.
43. Lee S, Cheong J, Lee J. Clinical application of autologous platelet-rich plasma (PRP) on delayed wound healing of a dog with burns. J Vet Clin. 2018;35(5):229-232.
44. López S, Vilar JM, Sopena JJ, Damià E, Chicharro D, Carrillo JM, et al. Assessment of the Efficacy of Platelet-Rich Plasma in the Treatment of Traumatic Canine Fractures. Int J Mol Sci. 2019;20(5):1075.
45. Andersen C, Wragg NM, Shariatzadeh M, Wilson SL. The Use of Platelet-Rich Plasma (PRP) for the Management of Non-union Fractures. Curr Osteoporos Rep. 2021;19(1):1-14.
46. Shafieian R, Matin MM, Rahpeyma A, Fazel A, Sedigh HS, Nabavi AS, Hassanzadeh H, Ebrahimzadeh-Bideskan A. Effects of Human Adipose-derived Stem Cells and Platelet-Rich Plasma on Healing Response of Canine Alveolar Surgical Bone Defects. Arch Bone J Surg. 2017;5(6):406-418.
47. Shafieian R, Matin MM, Rahpeyma A, Fazel A, Sedigh HS, Sadr-Nabavi A, Hassanzadeh H, Ebrahimzadeh-Bideskan A. The effect of platelet-rich plasma on human mesenchymal stem cell-induced bone regeneration of canine alveolar defects with calcium phosphate-based scaffolds. Iran J Basic Med Sci. 2017;20(10):1131-1140.
48. Martínez CE, Smith PC, Palma Alvarado VA. The influence of platelet-derived products on angiogenesis and tissue repair: a concise update. Front Physiol. 2015;6:290.
49. Dehghan MM, BaghabanEslaminejad M, Motallebizadeh N, Ashrafi Halan J, Tagiyar L, Soroori S, et al. Transplantation of Autologous Bone Marrow Mesenchymal Stem Cells with Platelet-Rich Plasma Accelerate Distraction Osteogenesis in A Canine Model. Cell J. 2015;17(2):243-52.
50. Catarino J, Carvalho P, Santos S, Martins Â, Requicha J. Treatment of canine osteoarthritis with allogeneic platelet-rich plasma: review of five cases. Open Vet J. 2020;10(2):226-231.
51. Robiony M, Polini F, Costa F, Politi M. Osteogenesis distraction and platelet-rich plasma for bone restoration of the severely atrophic mandible: preliminary results. J Oral Maxillofac Surg. 2002;60(6):630-5.
52. Bianchini E, Mancini F, Di Meo A, Stabile A, Buratta S, Moscati L, et al. Protective effects of platelet-rich plasma against lidocaine cytotoxicity on canine articular chondrocytes. Acta Vet Scand. 2018;60(1):63.

53. Cook JL, Smith PA, Bozynski CC, Kuroki K, Cook CR, Stoker AM, et al. Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. J Orthop Res. 2016;34(4):607-15.
54. Vilar JM, Manera ME, Santana A, Spinella G, Rodriguez O, Rubio M, et al. Effect of leukocyte-reduced platelet-rich plasma on osteoarthritis caused by cranial cruciate ligament rupture: A canine gait analysis model. PLoS One. 2018;13(3):e0194752.
55. Xie X, Zhao S, Wu H, Xie G, Huangfu X, He Y, et al. Platelet-rich plasma enhances autograft revascularization and reinnervation in a dog model of anterior cruciate ligament reconstruction. J Surg Res. 2013;183(1):214-22.
56. Abouelnasr K, Hamed M, Lashen S, El-Adl M, Eltaysh R, Tagawa M. Enhancement of abdominal wall defect repair using allogenic platelet-rich plasma with commercial polyester/cotton fabric (Damour) in a canine model. J Vet Med Sci. 2017;79(7):1301-1309.
57. Tobita M, Uysal CA, Guo X, Hyakusoku H, Mizuno H. Periodontal tissue regeneration by combined implantation of adipose tissue-derived stem cells and platelet-rich plasma in a canine model. Cytotherapy. 2013;15(12):1517-26.
58. Stambolsky C, Rodríguez-Benítez S, Gutiérrez-Pérez JL, Torres-Lagares D, Martín-González J, Segura-Egea JJ. Histologic characterization of regenerated tissues after pulp revascularization of immature dog teeth with apical periodontitis using tri-antibiotic paste and platelet-rich plasma. Arch Oral Biol. 2016;71:122-128.
59. Sharun K, Pawde AM, Manjusha KM, Banu S A, Kalaiselvan E, Kumar R, et al. Classification and coding of platelet-rich plasma derived from New Zealand white rabbits for tissue engineering and regenerative medicine applications. Expert Opin Biol Ther. 2021.