

Underlying factors that may affect the treatment of Platelet-rich plasma in chronic wounds

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Abstract. Platelet-rich plasma (PRP) has gained widespread usage in the treatment of various chronic wounds due to its ease of preparation and high safety profile. But not every treatment can achieve satisfactory results. The quality of PRP is based on individual biological characteristics. Autologous PRP technology is greatly affected by the patient himself. Individual responses to PRP treatment are different and will produce different therapeutic effects. Especially in patients with uncontrollable factors such as aging, diabetes, and coronary heart disease, the use of antiplatelet drugs may potentially reduce the quality of autologous platelet-rich plasma (PRP). When treating related diseases, it is important to consider the impact of factors such as age, gender, and the specific disease. Currently, many researchers are focusing on the development of allogeneic PRP technology to avoid the inconvenience of collecting autologous blood and reduce potential negative effects that may exist in the patient's disease itself. In this review, we explore the factors generally recognized in current research which influence the efficacy of PRP.

Keywords: platelet-rich plasma, chronic wounds, autologous, allogeneic

1. Introduction

In the past, various types of acute and chronic wounds were treated with traditional dressing changes, simple debridement, and closed negative pressure suction methods; or intraoperative treatment with

autologous skin grafts and various tissue flap repairs. However, traditional dressing changes and simple debridement treatment take a long time, the degree of infection in the body is difficult to control, and long-term antibiotic treatment is required. The use of various autologous skin grafts and tissue flap repairs not only has high surgical risks, long operation times, high economic costs, but also can easily cause serious damage to surrounding tissues. Therefore, there is an urgent clinical need for a treatment method with short wound healing time, simple and easy operation method, low treatment risk coefficient, and minimal damage to the body. The emergence of PRP has significant effects in repairing soft tissue wounds such as diabetic ulcers, vascular ulcers, pressure injuries and infectious wounds in early animal experiments and clinical practice.

Platelet-rich plasma (PRP) is a platelet concentrate extracted from whole blood (autologous blood or allogeneic blood) through high-speed centrifugation using the principle of gradient centrifugation. It is usually 3-8 times the normal platelet concentration of the human body [1], rich in supernormal physiological concentrations of platelets, white blood cells and fibrin [2]. Studies have shown that there are more than 800 kinds of proteins in PRP, including various active proteins, growth factors, exosomes, platelet microparticles, MicroRNA, etc. [3].

PRP stands out for its ease of preparation and high safety profile. Currently, autologous PRP technology has been widely used in various clinical fields, including orthopedics, maxillofacial surgery, sports medicine, burns and plastic surgery [4], especially in promoting the healing of chronic refractory wounds. [5]

2. Physiological mechanism of PRP-mediated wound healing

Wound healing is a complex and long process, which mainly includes the coagulation phase, inflammatory exudation phase, proliferation and migration phase, and matrix remodeling phase. PRP is mainly composed of platelets, white blood cells and fibrin. Platelets are rich in growth factors. The basic principle of PRP treatment of wounds is that injecting concentrated platelets at the injured site can promote tissue repair by releasing many bioactive factors, such as growth factors, cytokines, lysosomes, and adhesion proteins. Upon application to the wound site, PRP initiates the release of them. These factors are responsible for initiating the hemostatic cascade, synthesizing new of connective tissue and revascularization. In addition, there are reports that activated PRP can release a series of antibacterial substances, such as adenosine, histamine, immunoglobulin, etc., which have antibacterial effects and can reduce local inflammation and prevent wound infection [6] [7].

PRP contains a large number of chemokines and active proteins, which are involved in regulating inflammatory responses. When the inflammatory reaction is severe, PRP can inhibit the excessive inflammatory reaction by inhibiting the transcription and activity of inflammatory factors, inhibiting the gene sequence expression of C-X-C chemokine receptor 4 and antibacterial active substances such as fibrin peptide. A small number of white blood cells contained in PRP, through the regulation of various cytokines and biological proteins, chemotaxis, aggregation and activation of macrophages, neutrophils, etc., engulf pathogenic microorganisms, and the cells mediate immune responses and assist the body at the same time. Remove pathogenic microorganisms and necrotic tissue from wounds, thereby enhancing the body's local anti-infection ability and accelerating the regeneration and repair of damaged tissues.

3. Factors influencing PRP-mediated wound healing

The quality of PRP is based on individual biological characteristics. Autologous PRP technology is greatly affected by the patient himself. Individuals have different responses to PRP treatment and will produce different therapeutic effects, which depend on many endogenous and exogenous factors. , mainly including the following aspects: (1) Endogenous uncontrollable factors: donor's age, gender, metabolic diseases (including diabetes, obesity or hyperuricemia), etc., (2) Exogenous controllable factors : Centrifugal force, centrifugation time, activation method, type of activator, usage and dosage of PRP, etc. when preparing PRP. These factors may affect the ultrastructure of platelets. In particular, uncontrollable factors such as aging, diabetes, and coronary heart disease patients taking antiplatelet drugs may reduce the quality of autologous PRP. When treating related diseases, the effects of age, gender, disease, etc. must be considered. Currently, many researchers have Attention is paid to the development of allogeneic PRP technology, thereby avoiding the inconvenience of collecting autologous blood and reducing the potential negative effects that may exist on the patient's disease itself [8] [9]. However, whether PRP ultimately affects wound healing has not been well explored.

3.1. Age

In 2015, Salini V et al. used PRP to treat patients with refractory Achilles tendinopathy and found that compared with the young group, the number and function of tenocytes and tenoblasts were significantly reduced in the elderly group. The therapeutic effect of PRP in the elderly was greater. Poor [10]. In 2016, Middeldorp et al. explored the impact of age on PRP regenerative therapy. Using a mouse alloplastic model, they found that plasma from young animals could improve the basic physiological functions of muscles and livers in older animals, and could alleviate Alzheimer's disease. symptoms [11]. The mechanism by which plasma in young individuals regulates tissue regeneration may be related to the different contents of growth factors in plasma. Some studies have found that age is negatively correlated with PDGF-BB and IGF-1 in plasma [12]. In addition, another study used two different types of PRP obtained from young and old donors to treat rats with joint lesions and found that PRP derived from young donors showed better therapeutic effects [13]. In 2021, in order to study the differences between PRP from young and old donors, Diego Delgado and others extracted PRP from donors aged 65-85 and 20-25 years old, analyzed the cellular and molecular composition of the two PRPs, and subsequently used them in the central Cellular responses were evaluated in an in vitro model of the nervous system, CNS, and differences in proliferation, synaptogenesis, and inflammatory responses were studied. Although no differences were found in the cellular composition of the two PRPs, PRP from young donors showed more positive effects in the treatment of CNS diseases. effect [14].

3.2 Metabolic diseases

According to statistics, the incidence of chronic wounds, coronary heart disease, diabetes and other chronic diseases has increased sharply in recent years. Due to the body's own reasons or frequent use of drugs that may affect platelet function, these people are likely to affect the therapeutic effect of autologous PRP. Although there are quite a few studies showing that the use of PRP in patients with diabetes and coronary heart disease can achieve the desired results, hyperglycemia and coronary heart disease may lead to platelet activation and hyperplatelet function in patients. One study found that 24 days after hypoglycemia was induced in patients with type 2 diabetes, within hours, the body's sensitivity

to prostacyclin decreases, resulting in overactive platelet function [15]. During the preparation process of platelet concentrate products, the active ingredients are reduced due to early activation of platelets, thus affecting the therapeutic effect of PRP. However, there is still a lack of high-quality research on the specific efficacy of autologous PRP treatment in patients with diabetes and coronary heart disease. This makes it urgent to study the effects of age, diabetes, coronary heart disease and other factors on the release of active substances from PRP, so as to understand the effect of PRP treatment on such patients.

3.3 Activation methods and types of activators

PRP needs to be activated under certain conditions before it can work in the body. After PRP is activated, it will release a large amount of growth factors to promote wound healing. Different activation methods and types of activators may affect the release of growth factors in PRP, thereby affecting the effect of wound healing. Commonly used ways to activate PRP include adding thrombin or calcium chloride solution, repeatedly freezing and thawing PRP, and directly exposing it to collagen in the body. Depending on the activation method and type of activator, the bioactive components of PRP obtained are also different [16]. Studies have found that there are significant differences in the formation time, growth factor concentration and microvesicle concentration of thrombin and calcium ion-activated platelet gel. Calcium ion activators can slowly activate PRP, and the formed PRP gel retracts slowly and releases high the high content of FGF and high concentration of microvesicles are suitable for repairing joint cavity and sinus wounds. Thrombin can quickly activate PRP, and the formed PRP gel will retract quickly and release a high content of PDGF-BB and a certain concentration of microvesicles, which is suitable for acute trauma.

References

- [1] Gold, M.H., J.A. Biron, and W. Sensing, Facial skin rejuvenation by combination treatment of IPL followed by continuous and fractional radiofrequency. *J Cosmet Laser Ther*, 2016. 18(1): p. 2-6.
- [2] Mussano, F., et al., Cytokine, chemokine, and growth factor profile of platelet-rich plasma. *Platelets*, 2016. 27(5): p. 467-71.
- [3] Senzel, L., D.V. Gnatenko, and W.F. Bahou, The platelet proteome. *Curr Opin Hematol*, 2009. 16(5): p. 329-33.
- [4] Li, T., et al., Platelet-rich plasma plays an antibacterial, anti-inflammatory and cell proliferation-promoting role in an in vitro model for diabetic infected wounds. *Infect Drug Resist*, 2019. 12: p. 297-309.<富血小板血浆对痤疮丙酸杆菌的体外抑菌实验研究_吕品.pdf>.
- [5] Zhang, W., et al., Platelet-Rich Plasma for the Treatment of Tissue Infection: Preparation and Clinical Evaluation. *Tissue Eng Part B Rev*, 2019. 25(3): p. 225-236.
- [6] Anitua, E., et al., Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*, 2004. 91(1): p. 4-15.
- [7] Senzel, L., D.V. Gnatenko, and W.F. Bahou, The platelet proteome. *Curr Opin Hematol*, 2009. 16(5): p. 329-33.
- [8] Jeong, S.H., S.K. Han, and W.K. Kim, Treatment of diabetic foot ulcers using a blood bank platelet concentrate. *Plast Reconstr Surg*, 2010. 125(3): p. 944-52.
- [9] Perseghin, P., et al., Frozen-and-thawed allogeneic platelet gels for treating postoperative chronic

- wounds. *Transfusion*, 2005. 45(9): p. 1544-6.
- [10] Salini, V., et al., Platelet Rich Plasma Therapy in Non-insertional Achilles Tendinopathy: The Efficacy is Reduced in 60-years Old People Compared to Young and Middle-Age Individuals. *Front Aging Neurosci*, 2015. 7: p. 228.
- [11] Middeldorp, J., et al., Preclinical Assessment of Young Blood Plasma for Alzheimer Disease. *JAMA Neurol*, 2016. 18.3(11): p. 1325-1333.
- [12] Taniguchi, Y., et al., Growth factor levels in leukocyte-poor platelet-rich plasma and correlations with donor age, gender, and platelets in the Japanese population. *J Exp Orthop*, 2019. 6(1): p. 4.
- [13] Delgado, D., et al., Biological and structural effects after intraosseous infiltrations of age-dependent platelet-rich plasma: An in vivo study. *J Orthop Res*, 2020. 3.5(9): p. 1931-1941.
- [14] Delgado, D., et al., Effects of Platelet-Rich Plasma on Cellular Populations of the Central Nervous System: The Influence of Donor Age. *Int J Mol Sci*, 2021. 22(4).
- [15] Kahal, H., et al., Platelet function following induced hypoglycaemia in type 2 diabetes. *Diabetes Metab*, 2018. 44(5): p. 431-436.
- [16] Braun, H.J., A.S. Wasterlain, and J.L. Dragoo, The use of PRP in ligament and meniscal healing. *Sports Med Arthrosc Rev*, 2013. 21(4): p. 206-12.