Review Article

Potential benefits and applications of platelet-rich growth factors in wound healing

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ABSTRACT

Healing in tissues is a complex process which demands cellular organization mediated by a variety of signaling proteins and extracellular matrix for tissue repair. The understanding of this healing process at the microcellular level is incomplete. It is a well-proven fact that platelets have a significant role to play in wound healing. This review is a sincere effort to highlight the role of platelet-derived growth factors, the platelet concentrates and its various applications in wound healing.

KEY WORDS: Platelet-rich plasma, Platelet-rich fibrin, Platelet-rich growth factors, Platelet concentrate

INTRODUCTION

Wound healing is a complex highly coordinated event which is vulnerable to disruption leading to delayed healing or sometimes nonhealing of wounds. Proper wound care is vital to enhance the healing process.[1] Oral surgical procedures are highly dependent on efficient regeneration and healing, and one of the great tasks faced by clinical researchers is the development of bioactive surgical additives which regulates the inflammation and hastens up healing. Healing in tissues is a complex process which demands cellular organization mediated by a variety of signaling proteins and extracellular matrix for tissue repair. The understanding of this healing process at the microcellular level is incomplete.[2,3]

The main objective of the researchers in surgery is to get low invasiveness and a high standard of clinical healing.[4] It is a well-proven fact that platelets have a significant role to play in wound healing. They are known to release a range of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), fibroblast growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor, and insulin-like growth factors-1 (IGF-1) all of which helps in speeding up the healing process.[1] The use of these platelet concentrates, and its inherent properties have earned a heightened awareness in recent times for regeneration and promotes healing in soft and hard tissue healing in various dental treatments.[5]

The beneficial growth factors from platelets were first described by Ross *et al*.[6] Platelets trapped within fibrin matrix release growth factors after activation that stimulates the mitogenic response in the periosteum for bone repair.[2] It contains important growth-promoting factors such as PDGF, TGF-β, VEGF, and an epithelial growth factor that is responsible for increased cell mitosis, collagen production, and recruitment of other cells to the site of injury, thereby initiating vascular in-growth and cell differentiation.[7]

Platelet concentrates are defined as autologous or allogeneic platelet derivatives with a platelet concentration higher than baseline, and they are widely used in different areas of regenerative medicine to enhance wound healing processes.[8]

This review is a sincere effort to accumulate the literature on the various applications of platelet-rich growth factors; the platelet concentrates in healing.

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PLATELETS

Platelets the hemostatic cells perform a multitude of functions. They are produced in the bone marrow which is a small and discoid blood cell with a lifespan of 7–10 days. The normal platelet count ranges between 1.5 and 3.0 × 105/mL in circulating blood.[9] The platelets are composed of lysosomes, glycogen, the alpha-granules, and the dense-granules. Alpha-granules release many proteins when degranulated which have mitogenic growth factors, chemotactic and adhesion molecules, different cytokines, and hemostatic factors.[10]

The dense granules stored and released adenosine triphosphate (ATP), adenosine diphosphate (ADP), serotonin, and calcium ions.[11] The function of the ADP is to promote platelet aggregation, and the ATP acts on P2X1 and joins in the platelet response to the contact with the collagen under blood flow. Calcium is an indispensable cofactor which aids in platelet aggregation and transformation of fibrinogen to fibrin. It has an important regulatory part in wound healing; the calcium ions regulate the keratinocytes proliferation and its differentiation.[12] The serotonin is responsible for vasoconstriction and it increases the capillary permeability. Anti-inflammatory and pro-inflammatory effects are provided by the histamine. Lysosomes in platelets secrete cathepsin D and E, acid hydrolases, lysozyme, elastases, etc., which plays a significant role in the healing process.[3]

PLATELET CONCENTRATES

Isolated platelets from the peripheral blood are a source of autologous growth factors. This platelet concentrates serve as a grafting material in regenerative medicine due to its high contents of active molecules which act locally and helps in dense fibrin network formation, which consists of different cell types which promote healing.[13]

The fibrin glue formation by polymerizing fibrinogen with calcium and thrombin was first described in 1970. These fibrin adhesives can be acquired from the patient autologously, or it can be got from external sources, but when obtained from outside there is a small risk of disease transmission.[14]

The platelet concentrates increased amounts of growth factors to surgical sites which aid in tissue regeneration. As they attract undifferentiated cells and fibroblasts into the matrix which, in turn, triggers cell division by binding the cell membranes and growth factors leading to intracellular signal transduction.[15]

The role of platelet concentrate:[16]

1. It augments the healing of tissue, by increasing the proliferation of progenitors of the connective tissue which stimulate the fibroblast and the osteoblast activity and intern enhances the osteogenesis process.[17]
2. Platelet concentrated acts against bacterial oral infections due to its antimicrobial property.[18]
3. The signaling peptides in the platelet concentrates attract the macrophages and help in host defense.[19]
4. It also modifies the immune reaction with the help of interleukins which is released by the leukocytes.[20]

The main role of the platelet concentrate is to bring together various cells and elements of the tissue to induce and speed up the neoangiogenesis in the tissue. The grafted tissue acts in connecting the various cells to the matrix and to enhance angiogenesis which prevents necrosis and minimizes the risk of infection.[21] Platelet concentrate aids in both enhancing healings and also protects by quick wound closure.[22,23]

PLATELET-RICH PLASMA (PRP)

PRP is a platelet concentration of autogenous plasma. PRP is a platelet concentrate with a minimum of 1,000,000/1 L in a 5 mL volume of plasma, the normal platelet counts in the human blood normally range between 150,000/1 L and 350,000/1 L.[24]

Ross *et al*., in 1974, found that the by adding of calcium and platelets significantly improved the serum mitogenic capacity of whole blood. Later the use of PRP in various surgical fields, cosmetic surgery, soft tissue healing, nervous tissue, and burns, and bone healing was extensively studied.[24]

"PRP" first generation of platelet concentrates was first demonstrated, in 1988, by Marx *et al*. He demonstrated the benefits of platelet growth factors and the use of PRP in mandibular bone healing. It was established as a method to deliver the concentrated growth factors such as PDGF, IGF-1, and TGF-β to the surgical site, encasing the wound healing capacity and to stimulate bone regeneration.[25] Along with the procoagulant effect of PRP it is also a rich source of growth factors which helps in initiating the healing mechanism, and also it helps in sustaining the wound healing by speeding the bone repair, advancing the fibroblast proliferation and it also increases the tissue vascularity.

PRP preparation is done by a "two-step gradient centrifugation method." The first strong spin is used to separate the erythrocytes from the platelets, clotting factors, and leukocytes. Followed by the next step in which the platelet plug generating the PRP is separated in a second spin from the platelet-poor plasma which has 6–8 times the growth factors in comparison to the whole blood.[26,27] The last step is to activate the platelets using thrombin or calcium chloride to release the biomolecules.[27]

PRP has been studied extensively in dentistry. Research evidence concerning the efficiency and efficacy of PRP is controversial and still under study. The literature review of the effects of PRP in the socket after extractions has shown to improve both the soft tissue healing and bone healing. PRP has also shown positive healing in periodontal therapy when used as an adjuvant therapy along with other materials.[28,29]

Positive healing results are seen in implant surgery, using PRP. PRP is used in sinus lift procedures with significant results.[30] Along with bone curettage and application of PRP in the treatment of refractory BRONJ is very promising.[31] With its minimal risks to patients, easy to obtain, PRP can be utilized as a valid adjunct in many dental treatments.

PLATELET-RICH FIBRIN (PRF)

Choukroun *et al.* developed the PRF in 2001 at France and the production protocol of PRF attempts to accumulate platelets and released cytokines in a fibrin clot.[32]

Cytokines are immediately used and destroyed in a healing wound. The harmony between cytokines and their supporting fibrin matrix has much more unique importance than any other constant. A fibrin glue, enriched with cytokines (such as PRP) with large uncontrollable and short-term effect is less better than a physiologic fibrin matrix (such as PRF) with good and better effects.[14]

The first generation platelet concentrates, PRP showed promising results, yet, the complications of PRP such as cross infections and complexity of its preparation due to the use of bovine thrombin has led to the research on PRF that represents in the platelet gel healing concept, a new dramatic step.[33] It does not involve any agent to gelify like the PRP.[34]

Choukroun *et al.,* from France in the year 2001, developed the platelet-rich fibrin. The platelets and the leukocyte cytokines are the most crucial factors in the functions the biomaterial PRF, and the fibrin matrix which supports these factors released and serves as a resorbable membrane.[33] This membrane acts as a protective covering over the surgical site and fastens up the remodeling and integration of the healing.[35]

After activation of the platelets, the growth factors are released and are trapped inside the fibrin matrix, which stimulates the mitogenic response in the bone periosteum in the wound healing. The autogenous osteoinductive PRF material enhances the osteogenesis in the extracted tooth socket and hastens up the healing process.[35]

The preparation protocol of PRF is simple and similar to that of PRP. The 10 ml of the collected blood sample without anticoagulant from the patient is centrifuged immediately at a rate of 3000 rpm on a table-top centrifuge for 10 min. The centrifugation process yields, three layers in the test tube. The upper layer is the acellular platelet poor plasma, in the middle layer is the PRF clot, and the red blood cells (RBCs) settle at the bottom of the test tube. The middle PRF clot layer is then separated and removed from the other layers and later transferred on to a sterile dish. It is professed that the junction between the PRF and the RBC bottom layer is very rich in the growth factors.[34]

The autologous PRF researched shows to significantly improve healing in implant dentistry. It has been to be very effective in augmentation of the sinus floor. PRF plugs are also used in the healing of the extraction sockets. PRF is also used as a root coverage in gingival recession treatment procedures. The use of PRF and along with bone graft yields adequate results in the management of periodontic-endodontic furcation defect.[14]

CONCLUSION

This purpose of this review is to highlight the potential benefits and clinical applications of platelet-rich growth factors as reported in literature. The clinical researches on bioactive surgical additives have shown to regulate a number of extra-articular and intra-articular events hastening the soft tissue and hard tissue healing process. The deeper understanding of the entire process is recommended through more number of clinical trials to gain additional knowledge on the credibility and the efficacies of these platelet-rich growth factors.

REFERENCES

1. Shrivastava A, Shenoi R, Garg A, Vats V, Gadve V, Siddiqui A. Role of platelet rich fibrin in healing of extraction socket. Int J Contemp Med Res 2018;5:7-10.
2. Gassling V, Douglas T, Warnke PH, Açil Y, Wiltfang J, Becker ST. Platelet-rich fibrin membranes as scaffolds for periosteal tissue engineering. Clin Oral Implants Res 2010;21:543-9.
3. Harsini SM, Oryan A. Growth factor of platelet-rich plasma and its application in trauma and orthopedic surgery. EC Orthop 2018;9:139-46.
4. Agrawal M, Agrawal V. Platelet rich fibrin and its applications in dentistry – A review article. Natl J Med Dent Res 2014;3:54-61.
5. Kobayashi E, Flückiger L, Fujioka-Kobayashi M, Sawada K, Sculean A, Schaller B, *et al.* Comparative release of growth factors from PRP, PRF, and advanced-PRF. Clin Oral Investig 2016;20:2353-60.
6. Ross R, Glomset J, Kariya B, Harker L. A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells *in vitro*. Proc Natl Acad Sci U S A 1974;71:1207-10.
7. Dutta SR, Passi D, Singh P, Sharma S, Singh M, Srivastava D. A randomized comparative prospective study of platelet-rich plasma, platelet-rich fibrin, and hydroxyapatite as a graft material for mandibular third molar extraction socket healing. Natl J Maxillofac Surg 2016;7:45-51.
8. Piccin A, Di Pierro AM, Canzian L, Primerano M, Corvetta D,

Negri G, *et al.* Platelet gel: A new therapeutic tool with great potential. Blood Transfus 2017;15:333-40.
9. Vunjak-Novakovic G, Scadden DT. Biomimetic platforms for human stem cell research. Cell Stem Cell 2011;8:252-61.
10. Villela DL, Santos VL. Evidence on the use of platelet-rich plasma for diabetic ulcer: A systematic review. Growth Factors 2010;28:111-6.
11. Oryan A, Moshiri A, Meimandi-Parizi A, Maffulli N. Role of xenogenous bovine platelet gel embedded within collagen implant on tendon healing: An *in vitro* and *in vivo* study. Exp Biol Med (Maywood) 2015;240:194-210.
12. Stavropoulos A, Karring T. Five-year results of guided tissue regeneration in combination with deproteinized bovine bone (Bio-oss) in the treatment of intrabony periodontal defects: A case series report. Clin Oral Investig 2005;9:271-7.
13. Mihaylova Z, Mitev V, Stanimirov P, Isaeva A, Gateva N, Ishkitiev N. Use of platelet concentrates in oral and maxillofacial surgery: An overview. Acta Odontol Scand 2017;75:1-1.
14. Naik B, Karunakar P, Jayadev M, Marshal VR. Role of platelet rich fibrin in wound healing: A critical review. J Conserv Dent 2013;16:284-93.
15. Bhanot S, Alex JC. Current applications of platelet gels in facial plastic surgery. Facial Plast Surg 2002;18:27-33.
16. Del Fabbro M, Corbella S, Taschieri S, Francetti L, Weinstein R. Autologous platelet concentrate for post-extraction socket healing: A systematic review. Eur J Oral Implantol 2014;7:333-44.
17. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR, *et al.* Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.
18. Tang YQ, Yeaman MR, Selsted ME. Antimicrobial peptides from human platelets. Infect Immun 2002;70:6524-33.
19. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, *et al.* Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e56-60.
20. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, *et al.* Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part II: Platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e45-50.
21. Del Corso M, Vervelle A, Simonpieri A, Jimbo R, Inchingolo F, Sammartino G, *et al.* Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 1: Periodontal and dentoalveolar surgery. Curr Pharm Biotechnol 2012;13:1207-30.
22. Simonpieri A, Del Corso M, Sammartino G, Dohan Ehrenfest DM. The relevance of choukroun's platelet-rich fibrin and metronidazole during complex maxillary rehabilitations using bone allograft. Part II: Implant surgery, prosthodontics, and survival. Implant Dent 2009;18:220-9.
23. Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane. J Periodontol 2010;81:546-55.
24. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: From the wound healing to bone regeneration. Immun Ageing 2013;10:23.
25. Soffer E, Ouhayoun JP, Anagnostou F. Fibrin sealants and platelet preparations in bone and periodontal healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:521-8.
26. Peerbooms JC, van Laar W, Faber F, Schuller HM, van der Hoeven H, Gosens T, *et al.* Use of platelet rich plasma to treat plantar fasciitis: Design of a multi centre randomized controlled trial. BMC Musculoskelet Disord 2010;11:69.
27. 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.
28. Alissa R, Esposito M, Horner K, Oliver R. The influence of platelet-rich plasma on the healing of extraction sockets: An explorative randomised clinical trial. Eur J Oral Implantol 2010;3:121-34.
29. Ogundipe OK, Ugboko VI, Owotade FJ. Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars? J Oral Maxillofac Surg 2011;69:2305-10.
30. Anand U, Mehta DS. Evaluation of immediately loaded dental implants bioactivated with platelet-rich plasma placed in the mandibular posterior region: A clinico-radiographic study. J Indian Soc Periodontol 2012;16:89-95.
31. Coviello V, Peluso F, Dehkhargani SZ, Verdugo F, Raffaelli L, Manicone PF, *et al* Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients. J Biol Regul Homeost Agents 2012;26:151-5.
32. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunite en paro-implantologie: Le PRF. Implantodontie 2001;42:55-62.
33. Kanakamedala A, Ari G, Sudhakar U, Vijayalakshmi R, Ramakrishnan T, Emmad P. Treatment of a furcation defect with a combination 11. of platelet-rich fibrin (PRF) and bone graft – A case report. ENDO (Lond Engl) 2009;3:127-35.
34. Malathi K, Muthukumaraswamy A, Beri S. Periodontal 17. Regeneration of an intrabony osseous defect with combination of platelet rich fibrin and bovine derived demineralized bone matrix: A case report. IOSR J Dent Med Sci 2013;4:20-6.
35. Geeta IB, Galagali G, Kulkarni S, Suran P, Noushin F. A natural meliorate: Revolutionary tissue engineering in endodontics. J Clin Diagn Res 2013;7:2644-6.

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